CLINICAL PROFILE OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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With Partial fulfilment of the regulations

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(BRANCH VII)

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This is to certify that the dissertation titled **"CLINICAL PROFILE OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN"** submitted by **Dr.BALAMURUGAN.P** to the Faculty of Pediatrics, **THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI** in partial fulfillment of the requirements for the award of **M.D., DEGREE (PEDIATRICS)** is a bonafide research work carried out by him under our direct supervision and guidance.

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This dissertation entitled **"CLINICAL PROFILE OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN"** is a bonafide work done by **Dr.BALAMURUGAN. P** at Institute of Child health, Madras medical college, Chennai during the academic year 2016-2019 under the guidance of **Prof. Dr.SHANTHI, MD., DCH,** Professor of pediatric hematology, Institute of Child Health & Prof**. Dr.K.SUBRAMANIAN, MD., DCH,** Professor of Pediatrics, Institute of Child Health, Chennai – 600 008. This dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D., Degree in Paediatrics, Branch (VII).

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Dear Dr.P.Balamurugan,

The Institutional Ethics Committee has considered your request and approved your study titled **"CLINICAL PROFILE OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN" - NO.06072017**

The following members of Ethics Committee were present in the meeting hold on **07.07.2017** conducted at Madras Medical College, Chennai 3

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We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

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CERTIFICATE – II

This is to certify that the dissertation work titled **"CLINICAL PROFILE OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN"** of the candidate **Dr. BALAMURUGAN.P** with registration number **201617001** for the award of **M.D. PAEDIATRICS** in the branch of VII. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and the result shows 2 percentage of plagiarism in the dissertation.

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http://dspace.ut.ee/handle/10062/19037
https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4572835/

Instances where selected sources appear:

6

CONTENTS

ABBREVIATIONS

- AB - AB Blood Type
- ABL -Abelson murine
- ABO - Landsteiner's blood grouping system
- ALL- acute lymphoblastic leukemia
- AML- acute myeloid leukemia
- AML1 -acute myeloid leukemia 1
- ARID5B -AT-rich interactive domain-containing protein 5B
- BCR – break point cluster region
- BMI – body mass index
- CALLA – common ALL antigen
- CD – cluster of differentiation
- CDKN1B -cyclin-dependent kinase Inhibitor 1b
- CDKN2A -cyclin-dependent kinase Inhibitor 2A
- CEBPE -CCAAT/enhancer binding protein (C/EBP), epsilon
- CLL – Chronic lymphocytic leukemia
- CML – chronic myeloid leukemia
- CNS – central nervous system
- CR –complete remission
- CT – computed tomography
- dl - decilitre

- DNA – deoxyribo nucleic acid
- EFS – event free survival
- ERG -erythroblast transformation-specific related gene
- ETV6 – translocation Ets(E26) leukemia virus6
- FAB – French-american -british
- FISH -Fluorescence in situ hybridization
- Hb - hemoglobin
- HDL – high density lipoprotein
- HLA-DR -Human Leukocyte Antigen – DR
- HOX 11- homebox 11
- HOXA – homebox A
- Ig - immunoglobulin
- IGH -Immunoglobulin Heavy Locus
- IKAROS – interplanetary kite-craft accelerated by radiation of the sun
- IKZF1 – IKAROS Family Zinc Finger 1
- IL3 – interleukin 3
- JRA – juvenile rheumatoid arthritis
- kgs - kilograms
- L - litter
- LAK - lakhs
- LDH – lactate dehydrogenase
- LSCS – lower segment caesarian section
- LYL1 - lymphoblastic leukemia associated hematopoiesis regulator 1

- mg - milligram
- MLL -myeloid/lymphoid or mixed-lineage leukemia
- mm^3 – cubic millimeter
- MRD – minimal residual disease
- MRI –magnetic resonance imaging
- MYC -myelocytomatosis viral oncogene homolog
- n- number
- NHL –non hodgkins lymphoma
- NOS – not otherwise specified
- p – (petit)short arm of chromosome
- PAX5 -Paired box protein -5
- PBX1 – pre b leukemia transcription factor 1
- Ph – Philadelphia translocation
- q – long arm of chromosome
- RBC – red blood cell
- Rh - rhesus factor
- RT-PCR -Reverse transcription polymerase chain reaction
- RUNX1 –runt related transcription factor 1
- SD – standard deviation
- SGOT - serum glutamic-oxaloacetic transaminase
- SGPT -Serum glutamic pyruvic transaminase
- SVC – superior vena cava
- t -translocation

- TAL1 – T cell acute lymphocytic leukemia protein 1
- TCF3 – transcription factor 3
- TdT -terminal deoxynucleotidyltransferase
- TLS – tumor lysis syndrome
- TLX1 -T-cell leukemia homeobox protein 1
- USG - ultrasonogram
- WBC – white blood count
- WHO – world health organisation
- yrs - years

INTRODUCTION

Leukemia is one among the most commonly seen malignancy in children. Leukemia is characterized by neoplastic proliferation of hematopoietic stem cells and accumulation of blasts and immature cells in the bone marrow. Leukemia is classified as lymphoid or myeloid depending on the lineage of the progenitor cells involved. Depending on the natural history, leukemia is again classified into acute leukemia and chronic leukemia. Acuteleukemiais classified into Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL) [(1)].

The classification of acute leukemiais based on the cellular involvement of the primary stem cell defect. Defect in the maturation and differentiation of common myeloid progenitor cells produces acute myeloid leukemia. Acute Myeloid Leukemia is characterized by clonal expansion of myeloid blasts. On the contrary acute lymphoblastic leukemia is due to the defect in the maturation and differentiation of common lymphoid progenitor cell. Acute lymphoblastic leukemia is characterized by clonal expansion of lymphoid blasts in peripheral blood, bone marrow and other tissues.

More than 80% of the childhood cancer occurs in low and middle income countries. Cancer is the 9thmost common cause of death among children between 5 to 14 years in India [(2)]. Leukemia contributes to 40-50% of total childhood cancer. Indian data shows ALL accounting for 75-80% of paediatric leukemia. Second highest incidence of childhood cancer in India occurs in tamilnadu, after Delhi [(3, 4)].

ALL is the one of the most common childhood malignancies. It accounts for approximately 25% of all childhood cancers and 75% of all leukaemia worldwide [5]. 80% overall ALL occurs in children. About 2,500 to 3,500 new cases of ALL are reported in children each year in United States with an incidence of 31.9 cases per one million-person years. Most of the patients are younger than 5 years of age. ALL occurs in gender, age, ethnically and socioeconomically diverse population.

Paediatric ALL is the first disseminated cancer shown to be curable. On the contrary adults who are affected by ALL are experiencing devastating disease. Worldwide, the curative rate of childhood ALL is 90% in contrast to adults with a curative rate of 40 %[1]. In India 5 year survival rate is approximately 80 %[5, 6]. The cure rate in India is inferior to that of western countries. The reason for the low cure rate is manifold. These may include higher number of high risk population, limited data on cytogenetics, unfavourable cytogenetics to the drugs, increase incidence of relapse, febrile neutropenia, toxicity, and lower report of incidence and delayed diagnosis of disease[5].

The key for cure and overall outcome is based on early diagnosis and early treatment. The initial response to the first few weeks of remission induction chemotherapy is of paramount importance in predicting the long term disease survival. Since most of the childhood ALL occur in developing countries, the initial symptoms are encountered by the general physician and not by hemato-oncologists. Inadequate therapy and poor outcome of treatment

are sometimes due to delayed referral. The earliest presentation of ALL is often nonspecific, mimicking the common and self-limiting illnesses. This varied presentation of ALL presents a diagnostic challenge to the front line physician[7, 8].Knowing the incidence and early presentation of the disease in the local population is essential for early referral and thereby initiation of early treatment in the children. Hence this study mainly concentrates on the varied clinical presentations of ALL in children to aid in early suspicion of disease, thus enabling prompt diagnosis.

PATHOGENESIS

ALL is a neoplasm of precursor hematopoietic cells, B lymphoblast and T lymphoblast, involving bone marrow or other tissues like lymph node, thymus, with or without peripheral blood involvement. ALL is clinically, morphologically, immunophenotypically and genetically a heterogeneous disease.

ALL was thought to arise from exogenous or endogenous interactions, genetic susceptibility and chance mutation. This mutation causes developmental arrest of progenitor cells at a particular point in their differentiation and generates the capacity of uncontrollable self-renewal of cell. The first suggested causal exposure for childhood ALL is infection. The primary cause of paediatric ALL was chromosomal translocations occurring in utero during fet al haematopoiesis, the postnatal genetic events are the secondary contributors. Normal haematopoiesis and lymphoid development is disrupted by chromosomal rearrangements. Patient with trisomy 21, Klinefelter

syndrome and inherited diseases with excessive chromosomal fragility like Fanconi anaemia, Bloom syndrome and Ataxia telangiectasia have more risk for developing ALL. Acquired genetic changes is the most common mechanism of developing ALL whichis also said to be a hallmark of ALL[9, 10]. It includes aberrant expression of oncoprotein, loss of tumour suppressor gene and chromosomal translocation that generate fusion gene encoding transcription factor or active kinase.

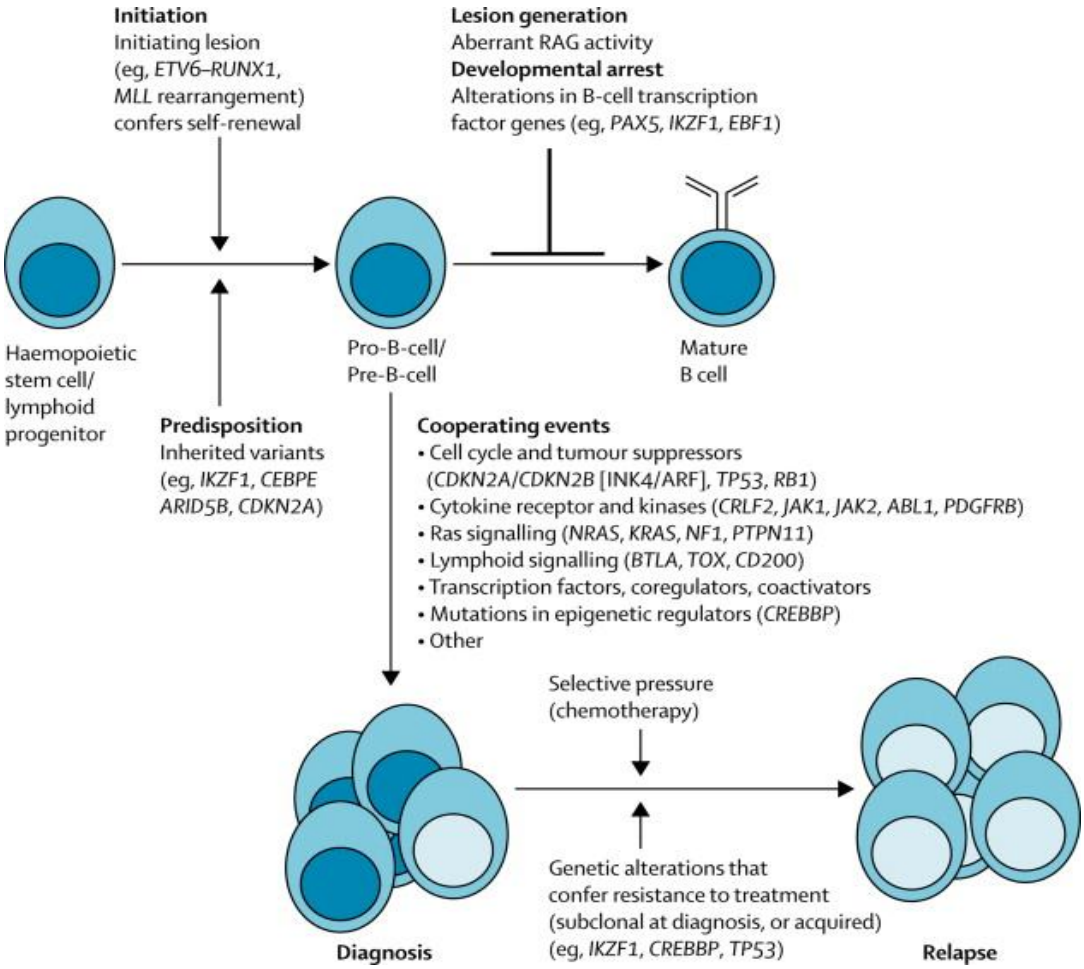


Figure 1

Leukemic transformation of cells needs genetic & epigenetic changes in key growth regulatory pathway and co-operative mutation. Leukemogenesis also needs multiple signalling pathway distribution. Leukemogenesis pathway is shown in figure 1. Majority of ALL patients have no gross chromosomal alterations which is suggesting that sub microscopic genetic alterations are likely to contribute leukemogenesis. The common allelic variants which are associated with childhood ALL are IKZF1, ARID5B, CEBPE, and CDKN2A.

Most frequent mutation seen in B cell ALL is PAX5 mutation. Function of PAX5 is encoding a paired domain protein which is required for the transition of pro B cell to pre B cell in B lineage. The second most frequent mutation is seen in IKZF1 gene. The IKZF1 gene encodes IKAROS zinc finger DNA protein. IKAROS zinc finger is needed for earliest lymphoid differentiation. 25% of B ALL shows t (12; 21) (p13; q22.3) translocation which usually have good prognosis. In this translocation ETV6 is fused to RUNX1. This translocation is often missed in routine karyotyping. Translocation t (1; 19) (q23.3; p13.3) is accounting for 5% of pre B ALL cases.PBX1 gene on chromosome 1q23.3 is fused with TCF3 gene on chromosome 19p13.3. The favourable cytogenetic patterns such as trisomies (trisomy 4 and 10) and translocation t (12; 21) are most common [9, 10, 11]. Development of normal B cell and development of leukemia in B cell pathway is shown in figure 2

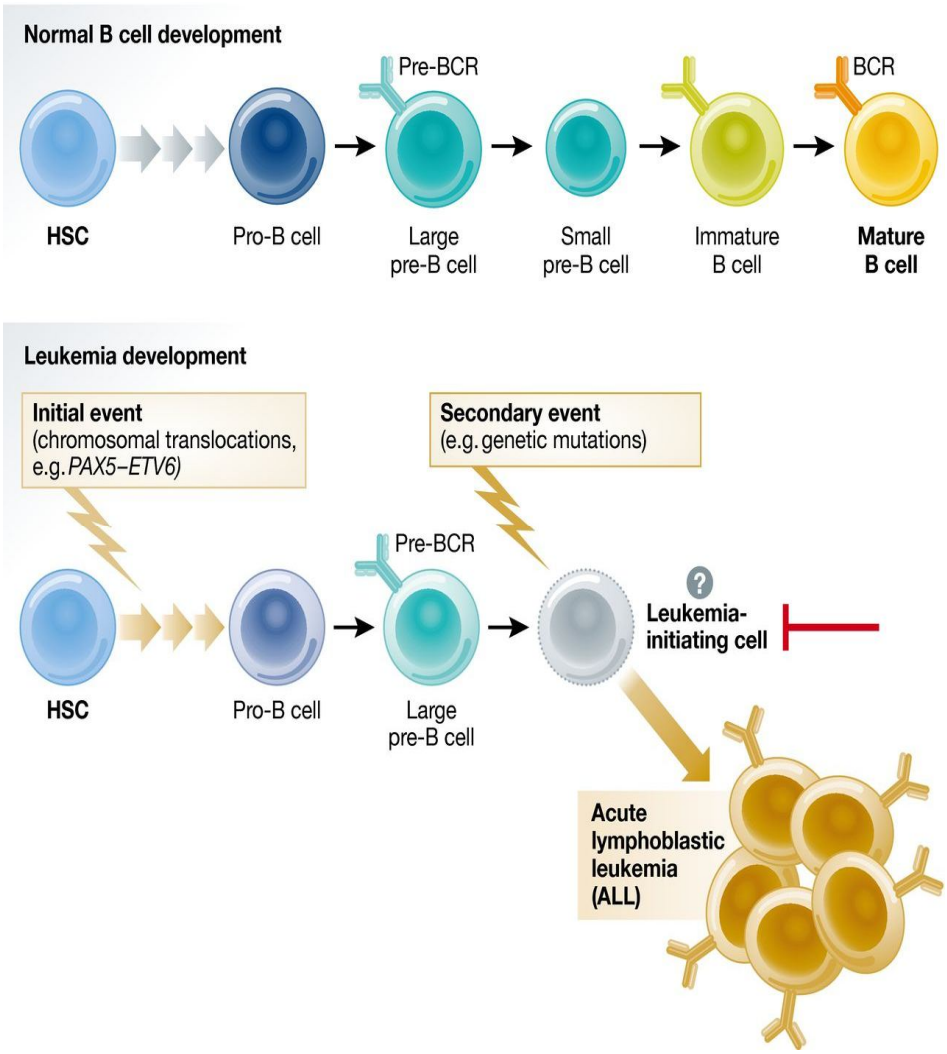


Figure 2

Development and maturation of B lymphocyte And development of ALL in B cell lineage. (HSC – hematopoietic stem cell)

Genetic alteration are having considerable prognostic values in treatment outcome. Table 1 shows prognostic value of genetic abnormalities in ALL.

Table 1

B cell ALL		
Chromosomal abnormalities	Genetic alteration	Prognosis
Trisomy 4, 10,17	-	Favourable
t(12;21)	ETV6-PBX	Favourable
Hyperdiploidy	-	Favourable
Hypodiploidy	-	Unfavourable
t(4;11)	MLL-AF4	Unfavourable
t(9;22)	BCR-ABL	Unfavourable
T cell ALL		
t(10;14)	TLX1/HOX11	Favourable

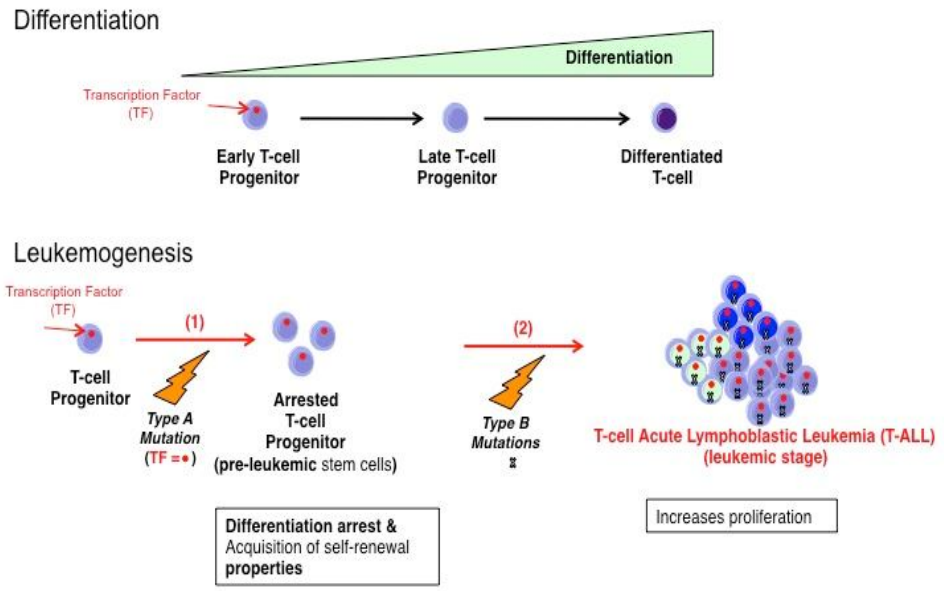


Figure 3

The NOTCH pathway mutation is seen in majority of T cell ALL. NOTCH1 is the regulatory protein which is synthesized as a single polypeptide protein. 60% of T cell ALL have activating mutation of NOTCH1[9, 10]. Cell cycle gene namely deletion of CDKN2A, deletion of RB1 and mutation in TP53 and CDKN1B are also involved in T cell leukemogenesis. The TAL1 gene deregulation is seen in 25% of T cell ALL. Other major group involved in T cell ALL leukemogenesis is homeobox gene. Overexpression of TLX1 deregulation of HOX11L2 and HOXA gene cluster is seen in T ALL. The normal development of T cell lineage and development of ALL in T lineage is shown in figure 2.

The other genetic abnormalities and their frequencies are shown in figure 4[(1)]

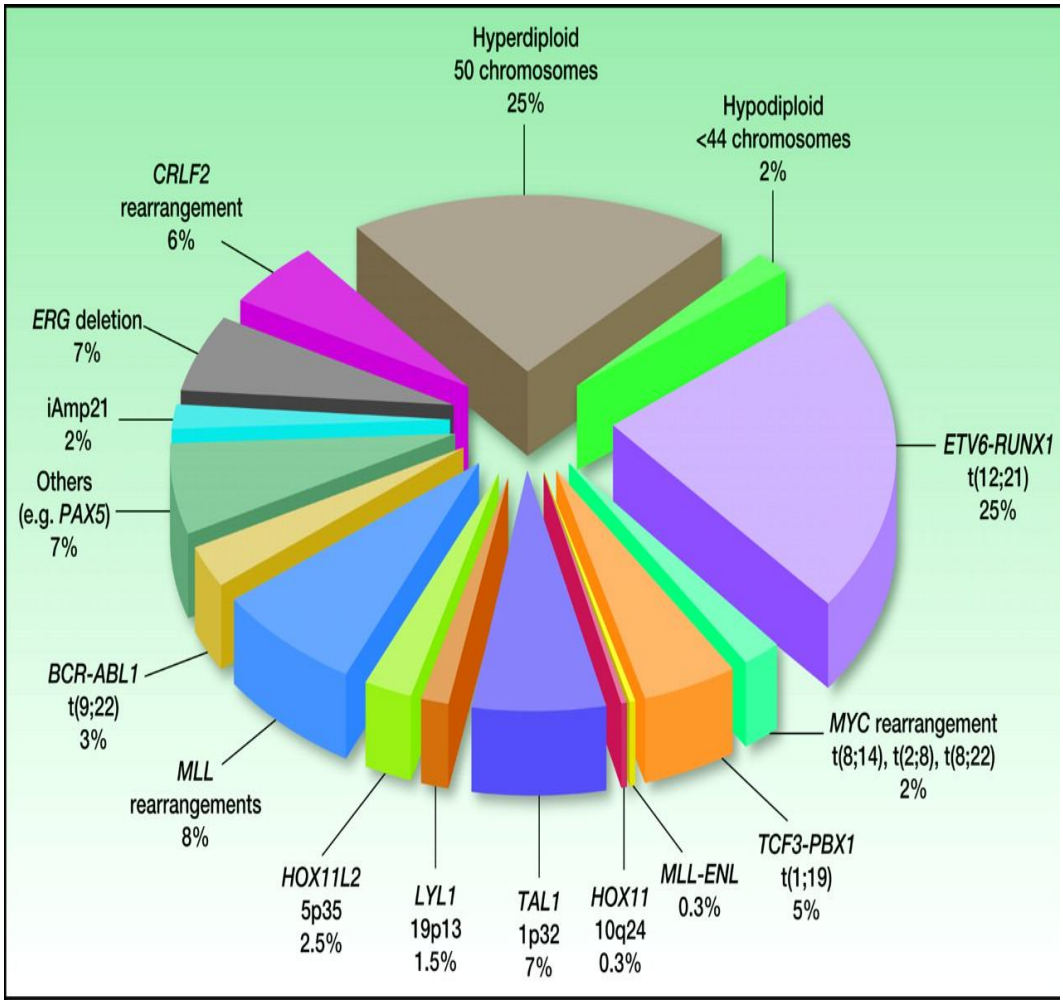


Figure 4

Frequency of specific genotype in childhood ALL.

RISK FACTOR

Childhood ALL is a complex disease caused by a combination of genetic predisposition and environmental exposure. ALL is not an inherited disease and does not tend to run in families and so a family member having the disease will not increase risk of other persons in the family for getting the disease. But there are few genetically inherited syndromes that tend to increase the risk of ALL [11, 12]. Genetic syndromes which have increased risk of developing ALL are as follows

Down syndrome

Fanconi anaemia

Shwachman-diamond syndrome

Bloom syndrome

Ataxia telengiectasia

Klinefelter syndrome

Diamond –blackfan anemia

Kostmann syndrome

Li-fraumeni syndrome

Severe combined immunodeficiency

Paroxysmal nocturnal hemoglobinuria

Neurofibromatosis type 1

Environmental risk factors

Out of the various environmental risk factors, only one environmental risk factor that is ionising radiation has been significantly linked to ALL. Most other environmental risk factor are not consistently linked or weakly associated with childhood leukemia. The possible risks of leukemia from being exposed to minor level of radiation such as imaging modalities (x ray) are not well known. But whenever an individual is exposed to high level of ionising radiation such as being suspected to radiation therapy or being exposed an atomic blast are convincingly associated with increased risk of ALL[13]. The other environmental risk factors which are of limited value in the development of ALL are as follows

Non ionising radiation

Alkylating agents -cyclophosphamide, ifosfamide, carboplatin, pesticide,

Epipodophyllotoxin- etoposide,

Teniposide,

Benzen.

Some of the in-utero or fet al factors have considerable risk of developing ALL. Increased risk of developing leukemia is noted in babies who were having birth weight of more than 4 kgs[10, 37]. Newer research says acceleration of foet al growth than the birth weights have strong association with developing ALL [38]. In utero exposures to X-ray have positive correlation with ALL.

PRESENTING CLINICAL FEATURES

Even though it affects all age groups, the highest incidence of B cell precursor ALL is observed in children between 1 to 5 years of age [14]. The peak incidence occurs between 3 to 4 years of age. Early peak is not seen in Americans and Africans and as a result ALL is more common with the children who are belonging to Caucasian descent. Children who are belonging to Hispanic ethnicity have the highest incidence of ALL, and polymorphism may contribute to both the increased risk of ALL for Hispanic children as well as their inferior outcomes [15].

ALL is more common among males than females [16, 17]. Patients with T cell ALL are tend to be older than with patients with B cell ALL.T cell ALL commonly affects the children belonging to median age group of 9 years and more commonly affects the male (75%) [18].

Symptoms and signs

Symptoms and signs occur because of bone marrow failure or the infiltration of medullary and extra medullary sites by leukemia. The onset of symptom is either insidious and slowly progressive over weeks to months or acute and explosive. In general, the more indolent the onsets of symptoms better the outcome. The varied clinical features of ALL are illustrated in figure 5.

Most common presenting complaints include fever, fatigue, lethargy, persistent, bruising or bleeding and bone pain. Lethargy and fatigue depends on the severity of anaemia.

Fever is of infectious or non-infectious origin which is often treated with broad spectrum antibiotics. Fever usually resolves with chemotherapy. Thrombocytopenia may be the cause of bleeding and bruising.

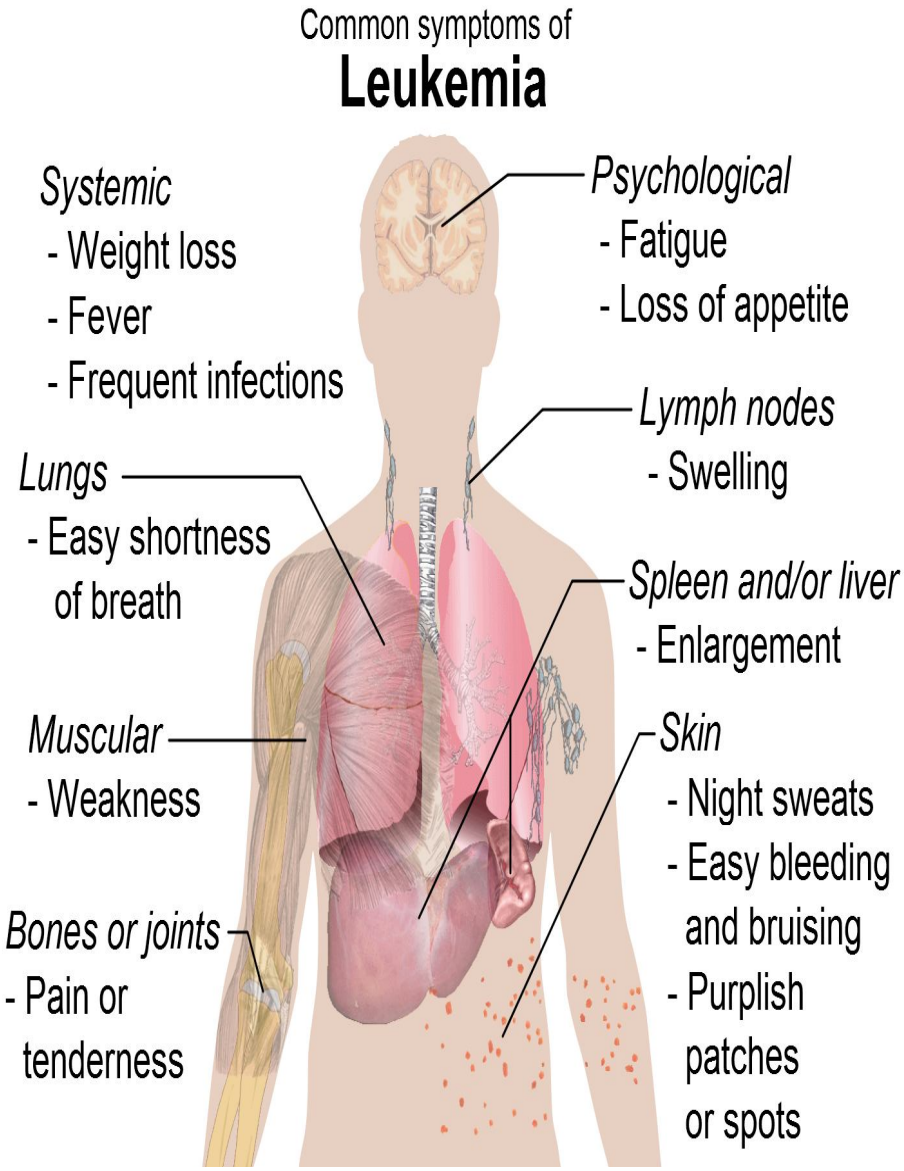


Figure 5

Bone pain is the most frequent presenting complaint which may occur as a result of bone marrow expansion, bone erosion, or leukemic periosteal involvement. Presenting complaint in young children will be gait disturbances or refusal to walk. Vertebral compression fractures may complicate generalized osteoporosis, leading to back pain. Prominent skelet al symptoms occur primarily in children without lymphadenopathy, organomegaly or leukocytosis and because of this presentation the diagnosis of ALL is delayed less commonly, bone pain are caused by recurrent episodes of bone marrow necrosis. Marrow necrosis is typically associated with a small leukemic burden and aleukemic blood picture. 5 percent of children with ALL may have bone pain or joint pain as a presenting symptom referred to rheumatology in suspicion of juvenile rheumatoid arthritis (JRA). Diagnosis is often delayed in these patients and the differentiation between ALL and JRA is critical to avoid pre-treatment with the corticosteroids.

Physical findings include pallor, petechiae or purpura, mucous membrane bleeding and fever. Extra medullary leukemic spread may manifest by lymphadenopathy which will be present in 50% of patients. Organomegaly will be frequently noted in imaging or examination but rarely symptomatic. Skin involvement will be rarely seen. If present, it will manifest as cutaneous nodules which is often seen in pre-B cell phenotype.

60% of patients with acute T cell ALL will have anterior mediastinal lymphadenopathy at the time of diagnosis which is rarely seen in children with B precursor ALL. The mediastinal mass of T cell ALL may be asymptomatic

and detected only on chest x-ray or may cause cough and dyspnoea on supine position. SVC syndrome occurs because of vascular compression by the anterior mediastinal mass, the clinical features will be facial swelling and plethora. Identification of symptomatic adenopathy is important prior to sedation for the diagnostic procedures such as bone marrow aspiration.

Microscopic infiltration of testis by ALL is common in males and it requires no treatment. Overt testicular involvement with leukemia presents as painless diffuse or irregular enlargement of testis which is of less significance in prognosis due to the availability of modern treatment with intense therapy.

CNS involvement will be seen in 2 to 3 percent of cases at the time of diagnosis and it is more commonly seen in patients with T cell ALL. Most patients with CNS involvement are asymptomatic and are only diagnosed with lumbar puncture. They are rarely symptomatic which includes headache, vomiting or cranial nerve palsies.

LABORATORY AND RADIOGRAPHIC FEATURES

60 percent of patients will have elevated WBC counts. Neutropenia will be frequently seen. Leukemic blasts are more commonly seen in patients with elevated WBC counts, they may be absent or found only after complete thorough review of blood smears from patients with decreased leukocyte counts. Increased WBC count of 50×10^9 /L is commonly associated with Lymphadenopathy, hepatosplenomegaly and T-cell immunophenotype. A WBC count more than 100×10^9/L is termed as hyperleukocytosis. Hyperleukocytosis associated ALL is rarely complicated by pulmonary insufficiency or intra cerebral haemorrhages.

Coagulopathies occur less commonly than AML but it is often associated with haemorrhagic or thrombotic complications. Coagulopathy commonly follows the administration of asparaginase and it is due to acquired anti-thrombin III deficiency leading to increased thrombin generation and it can be prevented by administration of anti-thrombin III

Tumour lysis syndrome may be seen in patients with large leukemic cell burden with high rate of cell turnover. Tumour lysis syndrome is associated with multiple metabolic disturbances; the most prominent of it is increased levels of serum uric acid, which will lead to urate nephropathy. Acute renal failure which occurs as a result of urate nephropathy may rarely be seen in initial presentation of disease, but it commonly follows the initiation of the anti-leukemic treatment. Diminished renal function may be seen in cases with leukemic infiltration of kidneys or it can be due to obstructive uropathy due to enlarged lymph nodes. Hyperphosphatemia and secondary hypocalcemia may cause precipitation of calcium phosphate in renal tubules which is followed by renal failure and hyperkalemia which will lead to cardiac arrhythmias or asystole. Recombinanturicase will break down the uric acid which has improved the treatment of tumour lysis syndrome. Serum Lactic dehydrogenase levels are increased due to increased turnover of leukemic cells. Early identification of tumor lysis syndrome will prevent the early death and complication such as ARF and cardiac arrhythmias, the diagnostic criteria for tumor lysis syndrome is given in table 2.

Table 2

TUMOR LYSIS SYNDROME–DEFINITION[19,20]	
LABORATORY –definition	
Two or more should be present within 3 days or up to 7 days following initiation of therapy	
Uric acid Phosphate Potassium Calcium Or ionised calcium	Above the upper limit of normal range for age in children, >8mg/dl in adult >6.5 mg/dl in children, >4.5 mg in adult >6.0 mEq/L <7.0 mg/dl or <1.12 mg/dl
CLINICAL– definition	
Kidney Cardiac Neurological	Acute kidney injury Increase in serum creatinine of 0.3 mg/dl (Or) Single value >1.5 timesthe upper limit of normal for age, in the absence of baseline value Oliguria –defined as an average urine output of <0.5 ml/kg/hours for 6 hours Arrhythmia , death seizure

Chest Radiographs of the patients with ALL will demonstrate anterior mediastinal mass in 5% to 10% of cases and it is most commonly seen in patients with T cell disease. The thymic masses are often associated with pleural effusion which are usually malignant and yield malignant cells in diagnostic thoracocentesis. Large mediastinal masses occurring in T cell ALL are medical emergency which requires careful monitoring and chemotherapy for preventing complications.

Skelet al lesions are demonstrated in X rays/CT/MRI of more than 50% of patients. The most common skelet al manifestation include radiolucent lines in the metaphysis of long bones adjacent to the provisional zone of calcification. Generalized rarefaction of bones, cortical and trabecular osteolytic lesions and periosteal new bone formation can be seen.

The presence of CNS disease at the time of diagnosis is an adverse factor in spite of intensification. Lumbar puncture will help in diagnosis of CNS involvement which will be present in 3% of children with ALL at the time of diagnosis. Cytocentrifugation (cytospin) of cerebrospinal fluid can be done in order to increase the diagnostic sensitivity by concentrating the low number of cells.

CNS involvement will be categorized into three types shown in table 3

The adverse prognostic significance associated with CNS2 disease. Traumatic lumbar puncture which have more than 10 erythrocyte/micro litre

and blasts at the time of diagnosis associated with increased risk of CNS relapse.

Table 3

Definition CNS for central nervous system involvement by leukemia	
Types	Finding
CNS 1	No blasts on cytospin
CNS II	Blasts on cytospin but CSF WBC<5 cells/microlitre
CNS III	Blasts on cytospin with WBC>or=5 cells /microlitre

Some of the children with ALL show life threatening complication at the time of diagnosis. Overwhelming infection and gram negative sepsis are most frequent life threatening complication. Bleeding due to thrombocytopenia cause stroke, pulmonary haemorrhage and gastrointestinal haemorrhages. Electrolyte imbalance is the anticipated complication of ALL and it may be present at the time diagnosis also. It may occur as an isolated one or combined one. It may also indirectly indicate the tumour burden. Acute airway obstruction often needs immediate resuscitation measures. Leucostasis is the most frequent complication encountered in initial presentation which is due to high WBC count. Usually WBC count more than 100×10^9/L will cause increase plasma viscosity and causing circulatory stasis of leucocytes. The

Leucostasis may cause stroke in children or pulmonary haemorrhage and may cause heart failure [21].

The complications and its underling pathology with the clinical presentation of those complications are summarised in table4

Table 4

Life threatening early complications		
Mechanism	Complication	Presentation
Neutropenia	Infection	Overwhelming infection, gram negative sepsis with or without disseminated intravascular coagulation
Thrombocytopenia	Bleeding	Stroke, pulmonary haemorrhage, gastrointestinal haemorrhage
Electrolyte imbalance	Blast lysis, acute renal failure	Hyperkalaemia, hyperphosphatemia, hyperuricemia
Reticuloendothelial infiltration	Mediastinal thymic mass	Acute airway obstruction
Increased plasma viscosity secondary to high WBC (more than 100×10^9/L)	Leucostasis	Stroke , acute pulmonary oedema, heart failure

DIAGNOSIS

Standard method of establishing diagnosis is by bone marrow aspiration and it also provides cells for morphological, histochemical, immunophenotypic, cytogenetic and molecular analysis.

PERIPHERAL SMEAR

Peripheral smear is the first and foremost clue for the diagnosis of ALL in children. Peripheral smear is the most economical way of initial screening of patients.FAB classification system had defined “acute leukemia as neoplasms with presence of 30% or more of blasts in peripheral bloodor bone marrow”. Many treatment centres considered ALL when there is more than 25%lymphoblast in peripheral blood or bone marrow[(22)].

Blasts have scant agranular cytoplasm, no Auer rods, coarse to fine chromatin, often indistinct nucleoli and no dysplastic myeloid cells. Others features commonly seen in ALL are leukoerythroblastosis with granulocyte precursors and nucleated RBCs, occasionally reactive lymphocytes and rarely marked eosinophilia

BONE MARROW EXAMINATION

Bone marrow examination is done for children showing less than 20% of blast in peripheral smear or those not showing blast in peripheral smear with classical clinical features suggestive of ALL. Slides should be stained with either Wright or Giemsa stain. The diagnosis of ALL is made when at least

20% lymphoblast are present in the bone marrow. Bone marrow hyper-cellularity and infiltration by lymphoblast is characteristic.

While doing bone marrow aspiration the utmost importance is provided for minimizing pain and fear of the child and the family, with the usage of conscious sedation or general anaesthesia. In case of ALL the marrow will be hyper cellular with replacement of fat spaces and normal marrow cells by means of leukemic infiltrates whereas in cases of AML the residual myeloid and erythroid precursors will appear morphologically normal. Megakaryocytes are reduced or absent in case of ALL.

The bone marrow lymphoblasts appear more homogenous with respect to the morphologic and biological characteristics than those present in blood. In case of failure of bone marrow aspiration due to increased cell density biopsy should be done, in such cases few other diagnostic modalities like flow cytometry can be used. It can replace marrow morphology, examination of peripheral blasts when present in sufficient quantity

FLOW CYTOMETRY

Flow cytometry is an important diagnostic modality in leukemia. Itplays a major role in evaluation of leukemic patients. The cell suspension is passed through a flow chamber and the light scattered by individual cells is detected by a photo detector. Specific antibodies labelled with fluorescent dyes are used. These antibodies will bind to the antigen of interest and emit fluorescent light

upon excitation. This is detected by means of a photomultiplier tube and finally quantified.

Flow cytometry enables rapid identification of ALL, quantification and immunophenotyping. It gives rapid and accurate diagnosis of ALL. Blood, bone marrow, lymph node, extra nodal tissues, and body fluids are used for flowcytometry.

IMMUNOPHENOTYPING

Immunophenotyping is an important tool in diagnosing ALL. It is also used for immunologic sub classification of ALL into T cell and B cell. Immunophenotyping can be done by performing immunohistochemistry or by means of multiparameter flow cytometry [1, 9, 10].

Immunophenotyping is based on the fact that different antigens which are expressed on the cells during each stage of normal haematopoiesis are also seen in the neoplasms that develop from the corresponding cells. Antigen expressed in B ALL and T ALL given in table 5.

Table 5

Immunophenotyping [1,9,10]	
Type	Antigen expressed
B-ALL	CD19, CD79a, CD22, CD10, CD24, PAX5, TdT, CD20, CD34
T-ALL	CD1a, CD2, CD3, CD4, CD5, CD7, CD8, TdT, CD99, CD34.

CYTOGENETIC STUDIES

Cytogenetic studies are needed to identify specific genetic alterations in leukemic blasts. Genetic alterations have the important prognostic value in ALL.

Table 6

Genetic abnormalities in Cytogenetic studies [9,10]	
Type of chromosomal abnormalities	Cytogenetic abnormality
Numeric abnormalities	Hyper diploid
	Diploid
	Hypo diploid
Structural abnormalities	Pseudo diploid
	t(9;22)(q34;q11)
	t(8;14), t(8;2), and t(8;22)
	t(4;11)(q21;q23) (and others involving 11q23)
	t(1;19)(q23;p13.3)
	4q11 abnormalities
	7q35 abnormalities
	Others

Cytogenetic studies gives the details of 'ploidy' which have important prognostic value. Cytogenetic studies detects the structural abnormalities in chromosome. Some of the cytogenetic abnormalities seen in ALL is tabulated in table 6

MOLECULAR STUDIES

Molecular studies will identify translocations more rapidly, it is useful in cases which are not detected on routine karyotype analysis, and molecular studies are also used to distinguish lesions that appear cytogenetically identical but are molecularly different. FISH, RT-PCR, Southern blot analysis are some of the examples for molecular studies used for subtyping ALL. Cytogenetic studies usually finds out changes in copy number or sequence of the nuclear DNA but molecular Genetic Expression Profiling is used to determine the level at which genes are expressed in samples compared with control. Expression profiling can be effective in classifying prognostically important subtypes including BCR-ABL1, TCF3-PBX1, HYPERPLOIDY, 11q23/MLL rearrangement, ETV6-RUX1 and over expression of the *Hox11* orphan homeobox gene which is detected in paediatric T-ALL was associated with excellent prognosis when treated with modern combination chemotherapy.

GENOME-WIDE ASSOCIATION STUDIES

Genomic wide association studies are emerging now recently. It can detect the presence of genetic changes which will not been found out by routine techniques e.g, activated tyrosine kinase pathways in Ph-like ALL, The clinical use of genome wide association studies is limited.

CLASSIFICATION

Classification of ALL plays a major role in choosing the treatment. The risk stratification method needs sub classification of ALL. Prognosis and treatment outcome are mainly dependent on the classification of ALL.

MORPHOLOGICAL CLASSIFICATION

The French-American-British classification is generally accepted morphological classification. According to the blast cell morphology, ALL is divided into L1 type, L2 type and L3 type [22, 23]. FAB classification and its features are shown in table 7.

Table 7

FAB classification [22,23]		
ALL subtype	Morphology	Frequency
L1	Small cell, scant cytoplasm, inconspicuous nucleoli	85%
L2	Pleomorphic large cell, more abundant cytoplasm, prominent nucleoli	14%
L3	Large round cell, Deeply basophilic cytoplasm and vacuoles	1%

Often the L1 and L2 blasts looks similar and are difficult to place on the classification. The revised FAB classification gives some histological score to distinguish the L1 type from L2 type. Histological scoring to distinguish the L1 and L2 subtypes is shown in table 8

Table 8

FAB scoring to distinguish L1 from L2[22,23]	
FAB type scoring: L1 v L2	Score
Nuclear: cytoplasmic ratio high in > 75% cells	+1
Nuclear: cytoplasmic ratio low in > 25% cells	-1
Nucleoli absent or inconspicuous in > 75% cells	+1
Nucleoli present in > 25% cells	-1
Irregular nuclear membrane in < 25% cells	0
Irregular nuclear membrane in > 25% cells	-1
Large cells <50% of total	0
Large cells > 50% of total	-1
Totals possible	+2 to -4
FAB type L1 = 0, 1, + 2; L2 = -, 2,-3,-4	

Due to advancement in immunophenotype studies, the FAB classification is no longer used [23]

IMMUNOPHENOTYPIC CLASSIFICATION

Immunophenotyping is done by flow cytometry with antigens expression in blast cells. The markers for various lineage is shown in table 9

Table 9

Immunophenotyping marker		
B lymphoid markers	T lymphoid markers	Multi-potent stem cell markers
CD19, CD10, CD20, CD22, cCD79a	CD3, CD5, CD7, CD1a,CD2, CD4, CD8, CD10, Cyt CD3	CD45, CD34, HLA-DR, TdT

For pro B ALL, CD 22 is more sensitive marker. CD10 is expressed in both lineage but more frequently expressed in B cell lineage than T cell lineage. It has significant prognostic value. CD10 expression in T cell ALL have good outcome and it can be taken as an independent prognostic factor regarding T cell ALL. But, in B cell ALL, CD10 cannot be taken as independent prognostic parameter[(23)].

WHO CLASSIFICATION

WHO proposed a classification based on morphology and cytogenetic profile in 1997 which was revised in 2008.Burkitt – cell leukemia was eliminated in 2008 WHO classification. According to WHO 2008 classification

three broad groups can be distinguished: precursor B-cell ALL, mature B-cell ALL and T-cell ALL. The guidelines mainly focus on precursor B-cell ALL and T-cell ALL, The sub classification of B-cell ALL are B-lymphoblastic leukemia/lymphoma, not otherwise specified (B-cell ALL NOS) and B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities. The B-cell ALL NOS may be divided further into early pre B-ALL, ALL and pre B- ALL. The sub-classification of precursor T-cell ALL is early T-cell ALL (pro T-cell ALL and pre T-cell ALL), cortical (thymic) T-cell ALL and medullary (mature) T-cell ALL [13]. B cell sub classification and characteristics are shown in table 10.

Table 10

B cell ALL sub classification by WHO	
ALL - Subtype	Characteristics
B-Cell ALL NOS	
Early Pre-B ALL/pro B-ALL	CD19+, cCD79a+, cCD22+, nuclear TdT positive, CD10-
Common ALL	CD10 (CALLA)
Pre-B ALL	Cytoplasmic IgM, CD19+, CD79a+, CD22+, CD10+

Cytogenetic abnormalities of ALL of WHO classification showed in table 11, table 12 and table 13.

Table 11

cytogenetic abnormalities[9,10]	
Hyperdiploidy	>50 and usually <66 chromosomes without structural abnormalities. Non-random: chromosomes 21, X, 14 and 4 most common; chromosomes 1, 2 and 3 being the least common. CD19+ve, CD10+. CD34+ (most cases) CD45 –ve (often). Patients with T-ALL should not be considered part of this group.
Hypodiploidy	< 44 – 46 chromosomes. Structural abnormalities are uncommon. CD19+, CD10+ Diagnosis may be missed by standard karyotyping due to endoduplication.
t(9;22)(q34;q11.2); BCR-ABL1	CD10, CD19, TdT positive, May express CD13/CD33. CD25 highly associated with t (9; 22). p190 transcript (most childhood cases) p210 transcript (50% of adult cases)

Table 12

cytogenetic abnormalities [9,10]	
t(v;11q23); MLL	Most common leukemia in infants. Short latency period. High WBC, CNS involvement. Pro-B immunophenotype CD19+, CD10 –ve, CD24 –ve, CD15+ve Neuroglial antigen-2 (NG2) relatively specific.
t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)	Rare in adulthood. CD19+ve, CD10+ve, CD34 +ve (commonly) May have near or complete absence of CD9/CD220/CD66c. Myeloid antigens (CD13) frequently expressed. ?necessary but sufficient for leukemic translocation?
t(5;14)(q31;q32);IL 3-IGH	Constitutive expression of IL-3 gene. Associated with eosinophilia which is reactive and not part of the leukemic clone. Diagnosis may be based on immunophenotype and genetic findings even if the bone marrow blast count is low. CD19+, CD10+
t(1;19)(q23;p13.3); E2A-PBX1 (TCF3 – PBX1)	CD19+, CD10+, cytoplasmic M heavy chain. Strong expression of CD9 Lack of CD34 or very limited CD34 expression.

Table 13

cytogenetic abnormalities[9,10]	
T-Cell ALL	
Precursor T- ALL	CD1a, CD2, CD3, CD4, CD5, CD7 and CD8. CD7 and cCD3 are most often positive. CD3 is lineage specific, CD4 /CD8 are frequently co-expressed; CD10 may be positive; CD79a (10% of cases) CD13/CD33 (19-32% of cases).
Pro T-cell ALL	cCD3+, CD7+, CD2-,CD1a-, CD34+/-; CD4-, CD8-
Pre T-cell ALL	cCD3+, CD7+, CD2+, CD1a-, CD34+/-; CD4-, CD8-
Cortical T-cell ALL	cCD3+, CD7+, CD2+, CD1a+, CD34-; CD4+, CD8+
Medullary T-cell ALL	cCD3+, CD7+, CD2+, CD1a-, CD34-, sCD34+; CD4+ or CD8+

2016 WHO classification is not a new classification rather it is the revision of 2008 publication based on the new knowledge of this disorder obtained since 2008.In this 2016 version to the list of recurrent genetic abnormalities two new provisional entities were added and the hypodiploidy was redefined as “either low hypodiploidy or hypodiploidy with TP53 mutation” [24]. The 2016 update WHO classification on ALL is shown in table 14 & 15

Table 14

WHO classification – 2016 update[24]
<u>B-lymphoblastic leukemia/lymphoma</u> B-lymphoblastic leukemia/lymphoma, NOS B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1 B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1 B-lymphoblastic leukemia/lymphoma with hyperdiploidy B-lymphoblastic leukemia/lymphoma with hypodiploidy B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1 B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like(Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21(Provisional entity)

Table 15

WHO classification – 2016 update[24]
<u>T-lymphoblastic leukemia/lymphoma</u> Early T-cell precursor lymphoblastic leukemia(Provisional entity) (Absence of CD1a/CD8, weak expression of CD5 Presence of 1 or more myeloid or stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65))

TREATMENT

Previously ALL remained to be a fatal childhood disease until effective pre symptomatic central nervous system therapy was developed in the year of 1960s. Even though combination chemotherapy provided frequent remissions, (disappearance of microscopically detectable leukemia in the bone marrow with recovery of marrow function), the appearance of leukemic cells in the CNS was common and the marrow relapse will occur despite further management).

Post induction intensification therapy has increased the 5 year event free survival (EFS) from 50% to nearly90% for children who are younger than 15years of age and it allowed replacement of cranio spinal radiation for most of the patients with an intra thecal therapy. Unlike other paediatric cancers curative therapy is available for ALL, outcomes are excellent with prolonged treatment which will be extended for 2 to 3 years or more than that. Treatment is tailored according to the risk of relapse, patients who are at the high risk of relapse will obtain aggressive treatment, whereas who are at low risk of relapse will obtain good outcomes even with less morbid treatment. Response to the induction therapy is assessed by multi parameter flow cytometry or PCR –based technology, now it supplements presenting clinical features and cytogenetic for treatment allocation.

The risk based stratification is one of the hallmark of the treatment of childhood ALL. This classification done based on risk of treatment failure with the features consistently affect prognosis. An Indian Childhood Collaborative Leukaemia Group Study for Childhood Acute Lymphoblastic Leukaemia gives risk stratification strategy which shown in table 16and table 17.

Table 16

RISK STRATIFICATION FOR T cell ALL	
Standard Risk(SR)	High Risk(HR)
WBC count of <100,000mm3 No bulky disease Not ETP-ALL Prednisolone Good responder CR at the end of induction.	WBC count ≥100,000/mm3 Prednisolone poor responder Bulky disease ETP immunophenotype T-NHL No CR after induction.

Table 17

RISK STRATIFICATION FOR B cell ALL		
Standard Risk(SR)	Intermediate Risk(IR)	High Risk(HR)
Age >1 and <10 years Non T-cell Prednisolone Good Responder No high risk cytogenetics WBC <50,000/mm3 MRD <10-3 after induction Complete Remission after induction No CNS disease	Good risk features but age ≥10 years Good risk features but WBC ≥50,000/mm3 Good risk features but bulky lymph nodes* MRD <10-3 after induction No High Risk criteria	All prednisolone poor responders, irrespective of age and presenting WBC count High risk cytogenetics CNS disease MRD ≥10-3 after induction
*(≥5 cm in peripheral region and in chest >5 cm on CT scan or occupying ≥1/3rd diameter on chest x-ray) and/or bulky liver/spleen reaching beyond midway to umbilicus and/or presence of testicular disease		

PHASES OF TREATMENT

ALL treatment approach varies to various risk groups. The key elements for treatment protocol includes remission induction, early intensification, consolidation, therapy directed to CNS, delayed intensification, continuation or maintenance therapy and allogeneic bone marrow transplantation.

Child should receive hyperhydration and allopurinol as soon as the diagnosis is made. This therapy minimizes the metabolic complications.

REMISSION INDUCTION

The goal of remission induction is to restore the normal hematopoiesis. This is done by rapid eradication of leukemic cell burden almost by 99%. This is achieved by three drug combination therapy which include glucocorticoid (prednisolone or dexamethasone), vincristine and L-asparginase.

Remission is defined by "less than 5% blast in marrow and return of neutrophil and platelet counts to near normal levels after 4-5 weeks of treatment"[(1)].

CONSOLIDATION

The goal of the consolidation therapy isto eradicate the sub microscopic residual disease that remains after complete remission, to maintain the remission in bone marrow and to reduce the risk of CNS relapse. This phase of chemotherapy involves combinations of different chemotherapeutic agents to maximize synergy and minimize drug resistance High dose systemic

methotrexate in parallel with intrathecal chemotherapy is used for consolidation. Other drugs are also which are mercaptopurine, thioguanine, cyclophosphamide, etoposide, and cytarabine.

INTENSIFICATION THERAPY

Intensification therapy is given mainly for high risk group of children. It can be associated with interim maintenance therapy. It will reduce the risk of relapse. It can increase the estimated 5 year survival rate compared with standard intensity treatment. It consists of reinduction and repetition of early induction phase.

MAINTENANCE THERAPY

Aim of maintenance therapy is reduce the minimal residual cells which are not detectable in current diagnostic technique. The therapy can continued up to two to three years. High incidence of relapse seen in children who had maintenance therapy of less than two years. The cornerstone of maintenance therapy is antimetabolite therapy with methotrexate and mercaptopurine. Continuous maintenance schedule have longer remission than interrupted maintenance schedule.

THERAPY DIRECTED AGAINST THE CNS

Although bone marrow remission could be achieved by using systemic chemotherapy, most children eventually develop CNS relapse in the absence of specific therapy directed toward CNS. Several methods are used to eradicate the CNS disease.

Intrathecal chemotherapy is one method to eradicate CNS disease which includes administration of intrathecal methotrexate or a combination of intrathecal methotrexate, cytarabine, and hydrocortisone (known as triple intrathecal agents). The other method is systemic administration of chemotherapy which includes dexamethasone, high-dose methotrexate, cytarabine, and asparaginase and cranial radiation

Summary of the treatment phases and duration is given in table 18.

Table 18

Phases of ALL treatment.		
Phases	Goal	Duration
Remission induction	Rapid eradication Restoration of normal hematopoiesis	4-6 weeks
Consolidation and therapy directed to therapy	To strengthen the remission in bone marrow Provide CNS prophylaxis	4-12 weeks
Intensification	Reducing the risk of relapse	8-12 weeks
Maintenance/continuation therapy	Reduce the minimal residual cells	2-3 years
Allogeneic bone marrow transplantation	Elimination of residual leukemic cells in high risk subtypes refractory to chemotherapy	

ALLOGENEIC BONE MARROW TRANSPLANTATION

Allogeneic bone marrow transplantation is advised to whom are refractory to chemotherapy. Total body irradiation and cyclophosphamide is used for myeloablation. Allogeneic hematopoietic stem cells are administered intravenously.

Allogeneic stem cell transplantation is the treatment which is also recommended for high-risk patients in complete remission. Philadelphia-chromosome-positive ALL patients have improved results with allogeneic bone marrow transplant.

REVIEW OF LITRATURE

1. Pandian G et al (2018) did a prospective study in 31 children who are diagnosed as leukaemia and treated for 3 years in GRH Madurai. Detailed history, clinical examination and lab investigations were done for those patients. The results of their study are ALL was the commonest leukaemia in children. Fever was the most common symptom, hepatosplenomegaly was the most common sign, T-cell leukaemia had worse prognosis compared to B-cell leukaemia and B- cell ALL was more common than T-cell ALL. Extra medullary organ involvement is an indicator of increased tumour burden and worse prognosis. Clinical and laboratory parameters did not predict the outcome in their study [(25)].

2. Siddaiahgari SR et al (2015) did an observational study on 103 children in tertiary health centre, India. The result of the study showed that initial symptoms will occur in children aged between 2 to 5 years, common clinical features are fever followed by pallor, hepatomegaly and splenomegaly. Most of the children in this study belong to standard risk according to their age, immunophenotyping, white blood cell count and cytogenicity[(6)].

3. Shalal HH et al (2017) conducted a retrospective study in 55 patients to show the initial presenting features of children with ALL. Fever and pallor were the most common features. Cutaneous bleeding, hepatosplenomegaly, lymphadenopathy, facial palsy, bone pain, anorexia, anaemia, mucocutaneous bleeding were the other features [(7)].

4. Guru FR et al (2018) conducted an observational study in the year between June 2008 to November 2013. In their study they evaluated the survival outcome in children with ALL and they determined prognostic factors like immunophenotyping, cytogenetic factors in addition to conventional factors which are associated with adverse outcome. Their studies clearly showed the prevalence of adverse prognostic factors were not very high in Indian population like which had been reported in previous Indian studies [(5)].

5. Sousa DW et al (2015) conducted a study in 76 patients who are under 19 years old and diagnosed as ALL. The result of their study showed that the most prevalent age group was 1-9 years, under 1 year old and over 9 year old patients accounted for 2.6 and 22.4 % respectively. Patients who were less than 1 year are associated with unfavourable prognostic factors. The unfavourable prognostic factors were high base line WBC count, pro B immunophenotype, and CD10 negativity. Patients who are between 1 and 9 years were associated with more favourable prognostic factors. The favourable prognostic factors were WBC count less than 50 x 10^9 cells /L, CD10 positivity, and DI >1.16. Commonly encountered clinical features were hepatosplenomegaly, fever and lymphadenopathy. CNS involvement and mediastinal masses were observed in 6.6 and 11.6% respectively. Anaemia was found in 85% of patients. B-immunophenotype ALL was found in 89.5% of patients, T-immunophenotype was found in 10.5% of patients [(26)].

6. Arya LS et al (2010) did a retrospective study in 60 children with T-cell ALL and 139 children with B-cell lineage ALL. The aim of their study

was to assess the clinical features, prognostic factors and outcome of childhood T-cell ALL in comparison with B-lineage ALL. The results were T- cell ALL was observed in 30% of cases. High risk factors at presentation were more than and equal to 10 years, WBC count > 50,000/mm^3, mediastinal masses and CNS leukemia. These high risk factors were more commonly seen with T-cell ALL compared to B lineage ALL. Even though high risk factors were commonly seen with T-ALL, the survival outcome was similar to B-lineage patients [(18)].

7. Pahloosye A et al(2011) conducted a prospective follow-up study of 100 patients in shahidsadoughi hospital in the period between march 2006 to February 2010. All the children included in this study showed abnormal blood count and 27% of children had pancytopenia, 37% had leukopenia, 38% had leucocytosis. White blood cell count of more than50000/mm3was detected in 22% of the children and 85% of children had anaemia. Most common presenting symptoms were lethargy, malaise, anorexia, pallor and fever. T cell ALL occurred more frequently compare to B cell ALL in this study group [(17)].

8. Khalid S et al (2015) reviewed the clinical details and treatment outcome of children in newly diagnosed acute lymphoblastic leukaemia. They did a retrospective study in children who were diagnosed with ALL and evaluated those patients for 17 years and the data was collected. 46 patients were diagnosed to have ALL during the study period and were on regular follow up. 45 of these were in complete remission after induction therapy for 28 days, 30 patients were doing well during the study period, among these 30

patients 26 remained relapse free, while only 4 got disease relapse, remaining 16 patients did not survive in whom 11 got disease relapse.[27]

9. Li SY et al (2015) compared the clinical features of ALL in male and female patients in southern china. 705 subjects were included in their study. Male were younger compare to female at the time of diagnosis. Male predominance was noted among the study group. Most frequently occurred blood group among the subjects is O blood group and also B-cell immunophenotype was most frequent than T-cell ALL immunophenotype and ALL most commonly presented between 2 years to 4 years [28].

10. Ahirwar R et al (2018) did this study to find out the actual incidence of four major types of leukaemia which are prevalent in India. Total 73 cases (in and out patients) were included in his study, out of those 73 cases on final diagnosis 23 patients had ALL, 11 cases had AML, 35 cases had CML, 1case had CLL and 3 were undiagnosed. Those undiagnosed cases were referred to tertiary care centre. His study revealed that the chronic leukaemia was more common than acute leukaemia. Among which chronic myeloid leukaemia was the most common type followed by acute lymphoblastic leukaemia, acutemyeloblasticleukaemia and chronic lymphocytic leukaemia respectively [29].

11. Khan AH et al (2015) conducted a prospective study in 75 cases who presented to oncology OPD and were diagnosed and documented to have acute leukaemia during the period from January 2009 to December 2011. Among 75 cases who were included in their study period AML comprised of 31 cases,

ALL comprised of 40 cases and biphenotypicleukaemia comprised of rest 4 cases. Out of 40 cases of ALL 29 cases had B-cell phenotype, the rest 11 cases had T-cell phenotype. B-cell ALL was commonly seen in children constituting 75.8%, while T-cell ALL was predominantly seen in adults. Immunophenotypic analysis revealed that the pro B-cell phenotype was encountered in 22 cases, mature B-cell in 7 cases and T-cell in 11 cases [(23)].

12. Sidhom I et al (2008) conducted a study in 67 patients who were newly diagnosed to have T-cell ALL. These patients were recruited from children's cancer hospital from Egypt during the time period of July 2007 to June2008. The results of their study were the frequency of CD34 was 34.9%, CD10 was 33.3%, while CD13/CD33 was 18.8%. There was no significant association encountered between CD34, CD10 or myeloid antigen positivity and presenting clinical features such as age, sex, TLC and CNS leukaemia. [(30)]

13. Anoop c et al (2016) did a retrospective analysis in southern India to determine the profile of ALL in children up to 2 years of age. Male predominance was observed and 18% of ALL was noted in infants. Fever was the most common presenting symptoms followed by pallor and hepatosplenomegaly. 35% of children had Severe anaemia (haemoglobin<7gm %), 28% had more than 50000/mm3 of WBC count and severe thrombocytopenia was noted in 20% of study population. Elevated LDH and uric acid was seen in 64% and 11.5% respectively. B cell immunophenotype most commonly occurred than T cell immunophenotype [(31)].

14.Badira, C.P et al (2016) did a retrospective study about the clinical profile and outcome of early T-cell precursor ALL. Their study result showed occurrence of Early T-cell Precursor ALL among T cell ALL was 16% with male predominance. Hyper leucocytosis was observed in 36.7%. Higher median age and minimal disease burden was noted in Early T-cell Precursor ALL in this study [32].

15. Baviskar JB et al (2016) conducted a prospective and retrospective study in 156 patients over a period of 5 years between may 2006 to may 2011. Diagnosis of ALL was based on peripheral blood count, peripheral blood smear and bone marrow examination for morphology. Cytochemistry study was done whenever required. In their study the commonest leukaemia was CML, followed by ALL, AML and then CLL. Out of 156 cases 90 were male and 66 were female. ALL was the most common type of leukaemia in children and adolescents whereas myeloid leukaemias were common in adults [14].

16. Kulkarni KP et al (2013) did a study to assess the gender ratio of ALL at a tertiary care centre in India. Their study result reported that male predominance was observed in childhood ALL in Indian population. This male predominance is not significantly different compare to world population [16].

17. Tavasolian et al (2014) carried out a case control study to establish the relationship between ABO blood group and ALL. Case and control group consist of 293 and 300 cases respectively. Their study result was AB blood group population was having higher risk of ALL compared to other blood group [33].

18. Kumar N et al (2017) did a retrospective analysis of nutritional status in 51 children who had completed the treatment in tertiary centre, south India. Nearly 50% of study population shows under nutrition at the time of diagnosis obviating the need for nutritional rehabilitation. Few children are becoming overweight and obese during the course of treatment signifies the need for modification in lifestyle and endocrine evaluation [34].

19. Yhigashiyama et al (2014) did a retrospective study to assess the nutritional status of ALL patients during chemotherapy. 23 patients who were diagnosed to have ALL are included in this study. At the time of diagnosis, 8.7% were underweight and 21.7% were overweight according to BMI Z score. According to waterlow score five patients were underweight and 3 were overweight, the prevalence of malnourished children did not change significantly during treatment [35].

20. Adelmen AS et al (2005) examined the incidence of ALL among children less than 5 years in United States. Country based incidence rate were analysed and they found that higher incidence of ALL was observed in urban area than rural area [15].

21. Totadri S et al (2016) did a retrospective analysis in tertiary care centre to study if the distance between the home and treating hospital will influence the outcome of children with ALL. The results are patients who are residing from rural and urban areas do not have significant difference in their survival [36].

22.Caughey RW et al (2008) did a meta-analysis to establish the relationship between the childhood ALL and birth weight. 32 studies and 16501 cases of leukaemia were included in this study. Among the leukaemia cases, 10974 cases were ALL. Significantly positive association was noted between high birth weight and ALL in this study and there were no association between ALL and low birth weight [37].

23. Milne E et al(2013) did a meta-analysis of data from 12 case control studies. The study aim was to establish the association between foet al growth velocity and risk of ALL. Cases and control in this study were 1680 and 3139 respectively. In this study positive association had been observed between increased risks of ALL and accelerated fet al growth [38].

24. Kong SG et al (2014) did a study regarding hyperleukocytosis in paediatric ALL at pusan national university hospital. Total enrolment for this study was 104 children. Twenty (19.2%) of 104 children had initial leukocyte count of $>100x10^9$/L, 11 patients had a leukocyte count of $>200x10^9$/L. Tcellphenotype, massivesplenomegalyand male gender were strongly associated with hyperleukocytosis .Patients who had initial leukocyte of $>200x10^9$/L had a lower EFS than those with initial leukocyte counts 100-$200x10^9$/L. The outcome of initial leukocyte count of $>200x10^9$/Lwere very poor [39].

25.İrken G et al (2006) conducted a study named “hyperleukocytosis in childhood ALL: complication and treatment outcome”. This study evaluated the outcome of ALL with respective of hyperleukocytosis ($>100\times10^9$/L). 18%

of this study population had hyperleukocytosis. This study result showed hyperleucocytosis had poor treatment outcome in ALL [40].

26. Sevinir B et al (2011) conducted a study to examine the incidence and outcome, of ALL and non-Hodgkin's lymphoma. 214 children had ALL in this group in which 26.5% had hyperuricemia and 0.47% had tumor lysis syndrome. Hyperuricemic ALL children of this study had high tumor burden which affected the treatment outcome adversely [41].

27. Clarke RT et al (2011)did a prospective study, in their study they screened 12303 abstracts for eligibility criteria and included 33 studies (n=3084) in the analysis. All were cohort studies without control groups. They identified 95 presenting signs and symptoms and ranked according to their frequency. More than 50% of children had five features : hepatomegaly (64%), splenomegaly (61%),pallor (54%),fever (53%),and bruising(52%).the additional features which were seen in a third to half of a children were recurrent infections (49%), fatigue(46%),limbpain(43%), hepatosplenomegaly(42%),bruising/petechiae(42%),lymphadenopathy(41%),bl eeding tendency (38%)and rash (35%).6% of children are asymptomatic during the diagnosis of ALL. Hepatosplenomegaly, pallor, fever or bruising will be seen in 50% of children. Abdominal distension, anorexia, weight loss, abdominal distension were the common abdominal symptoms. Joint pain and limp were the common musculoskelet al features. Unexplained illness in children require a thorough history and detailed clinical examination which

include abdominal examination, palpation for lymphadenopathy and careful examination of skin [8].

28. Kulkarni KP, et al (2013) did a study to find out the clinical correlation, prognostic impact of pancytopenia in ALL children with their survival. The study shows pancytopenia at the time of diagnosis had significantly better outcome than others[42].

29. AL Sudairy R et al (2013) conducted a retrospective analysis study. 594 patients were studied. Male predominance observed (56.4% of boys). The median age was 4.37. B cell ALL was observed in 89.5% and T cell ALL was observed in 10.5% [45].

STUDY JUSTIFICATION

- The clinical profile of acute lymphoblastic leukemia in Indian children is varied and also there is limited data.
- This varied presentation of ALL presents a diagnostic challenge to the physician.
- Overall outcome is based on early diagnosis and early treatment. The initial response to the first few weeks of remission induction chemotherapy is of paramount importance in predicting the long term disease survival.
- This study is done to analyse the clinical profile of acute lymphoblastic leukemia in paediatric patients and to reduce morbidity and mortality by early diagnosis and appropriate treatment.

AIM AND OBJECTIVES

- To determine the clinical profile of acute lymphoblastic leukemia in children between 1 month -12years of age at a tertiary care centre - Institute of child health and hospital for children, Chennai, south India.

MATERIALS AND METHODS

- STUDY DESIGN:

  Observational study

- STUDY POPULATION:

  Children in study age group admitted in haematology and paediatric medical ward, satisfying the inclusion criteria.

- PLACE OF STUDY:

  Department of haematology and paediatric medical ward in Institute of Child Health &Hospital for Children, Chennai.

- STUDY PERIOD:

  August2017 to September 2018.

- SAMPLE SIZE:

  One hundred and thirteen children (admitted consecutively in institute of child health & hospital for children with ALL are included in my study).

- INCLUSION CRITERIA:

  All children aged 1month to 12years diagnosed as acute lymphoblastic leukemiain Institute of Child Health &Hospital for Children, Chennai.

- EXCLUSION CRITERIA:

  Children with acute lymphoblastic leukemia who have started treatment outside, children with relapse of acute lymphoblastic leukemia, children with other haematological malignancy and children with other malignancies.

PROCEDURE

Informed consent from the parent/guardian was obtained. Detailed information was collected regarding various patient demographic characteristics including detailed history, clinical examination findings and laboratory parameters.

Detailed history taken in this study included fever and its duration irrespective of the admission in hospital, pallor, icterus, lymphadenopathy which was asked for by history of any swelling in the neck, axilla or groin region and was confirmed by clinical examination. The presence of rash and its type including infective, petechial or purpuric rash and abdominal distension for hepatomegaly, splenomegaly, ascites and mass was asked for. Swelling anywhere in the body other than lymphadenopathy and abdominal mass, especially in the cheek for parotid involvement was asked and confirmed by clinical examination., fatigue often not told by children but noticed by the mother. Abdominalpain, body ache, joint pain, difficulty in walking, bone pain was asked for and was confirmed by the presence of tenderness. Bleeding in the form of epistaxis, ecchymosis, gum bleed, melena, hematochezia, and hematemesis was asked for. History of seizures for the involvement of central

nervous system and any testicular swelling was asked for and confirmed by physical examination.

Past history of any underlying disorder that might predispose to the development of malignancy or syndromic disorder was obtained. Antenatal history and birth history including mode of delivery (delivered by labour natural or assisted mode or LSCS) was obtained. Birth weight was enquired from the mother and verified with relevant documents. Developmental history was asked and confirmed by developmental assessment. Family history including consanguinity and similar illness in the family members was obtained.

Nutritional status of the child was arrived at by measuring the height and weight. Length was used for children aged less than two years instead of height. Weight for height was calculated in children aged less than five years of age and BMI was calculated for children more than five years of age. The anthropometric measurements were plotted in the growth chart to look for malnutrition.

The history of initial symptoms was asked. Details regarding the time taken for the initial hospital visit where ALL was suspected and referral details were noted. The time taken for diagnosis from the appearance of initial symptoms was calculated in days.

All the children then underwent initial investigations like complete blood count, peripheral smear, blood sugar, renal Function Test (serum urea, serum creatinine), serum electrolytes (serum sodium, serum potassium), liver

function tests (SGOT, SGPT), Serum uric acid, Serum Amylase, Serum LDH, Lipid profile(serum triglyceride, serum LDL ,serum HDL) and urine routine.

Imaging modalities including X-ray chest, X-ray long bones, USG abdomen, and echocardiography are done. Blood culture and urine culture were done to rule out infective causes and to decide upon the choice of treatment. Serum viral markers, mainly hepatitis panel was done.

Children who are suspected cases of ALL with classical symptoms and signs were confirmed by bone marrow examination and CSF analysis for malignant cells.

The bone marrow examination and CSF tapping were done after obtaining informed consent from the parents. The diagnosis was confirmed by flowcytometric analysis of peripheral blood or bone marrow aspirate. Further, immunophenotyping was also done by using the flow cytometry.

All the above data were entered in a pre-structured Proforma.

Ethical consideration:

This study does not include any experimentation. Patients are informed of the procedure done in detail and informed consent is obtained. No one received any benefit, personal or professional from a commercial party directly or indirectly including the subject of this study.

STATISTICAL ANALYSIS:

Data was entered in excel sheet. Descriptive statistics analysis was done.

RESULT

A total of 113 children with ALL were included in this study

DEMOGRAPHY

73.45 %(83) of the children in this study group belong to rural area and 26.55 %(30) of children were from urban area. The distribution of residential places is illustrated in figure 6.

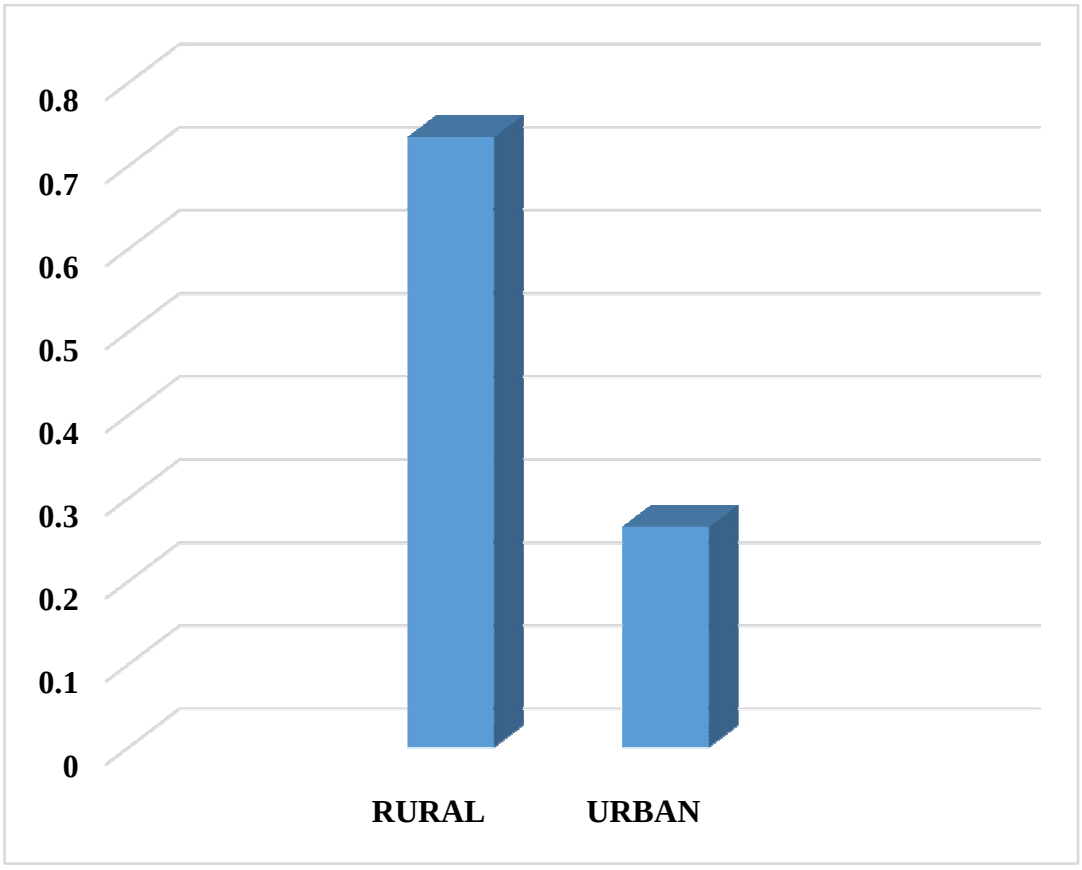


Figure 6

SEX DISTRIBUTION

Out of 113 children, 60.20% are boys and 39.80% are girls. Male: female ratio was 1.58:1. The sex distribution is shown in figure 7.

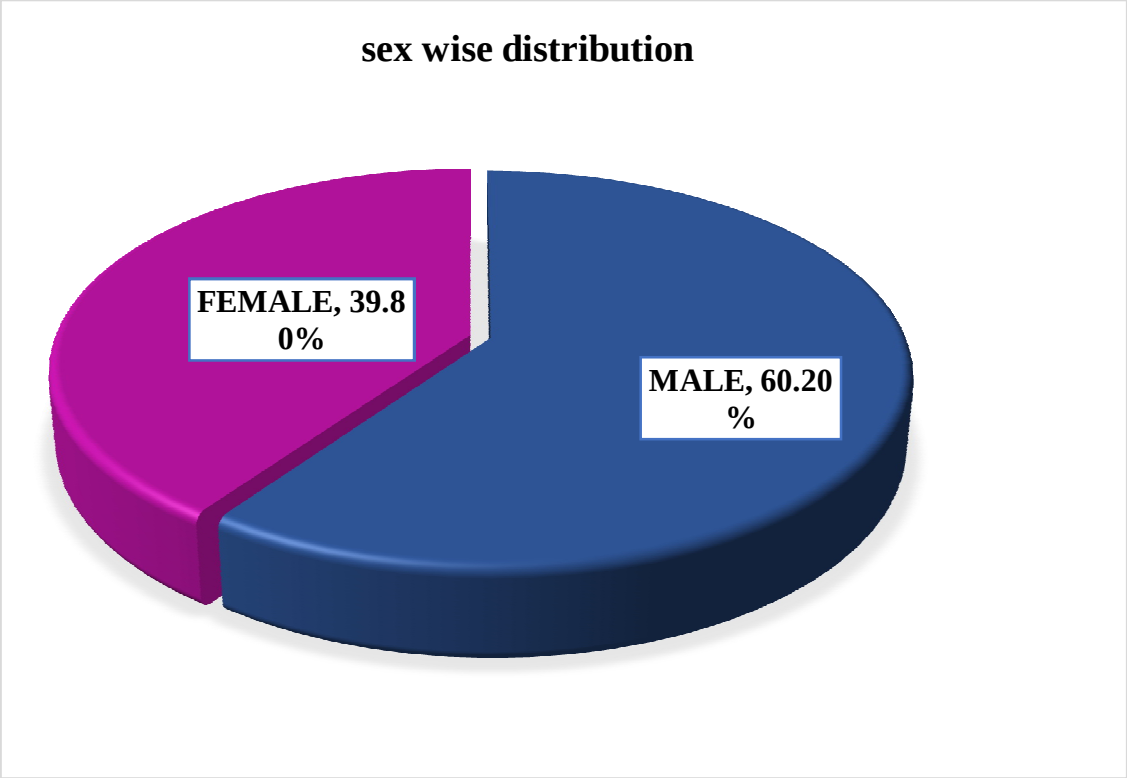


Figure 7

Sex distribution according to immunophenotyping is shown in table18. Children with B cell ALL were 91 .Males constituted 54.94 %(50) and females were 45.05 %(41). The Male: female ratio was 1.21:1.Total no. of children with T cell ALL are 22, among them 81.81 %(18) are maleand 18.18 %(4) were female children. Male: female ratio was 4.5:1

Table 19

Sex distribution				
	TOTAL	**MALE**	**FEMALE**	**M:F**
ALL cases	113	68(60.20%)	45(39.80%)	1.51:1
B cell ALL	91	50(54.94%)	41(45.05%)	1.21:1
T cell ALL	22	18(81.81%)	4(18.18%)	4.5:1

The immunphenotypic sex distribution is illustrated in figure 8.

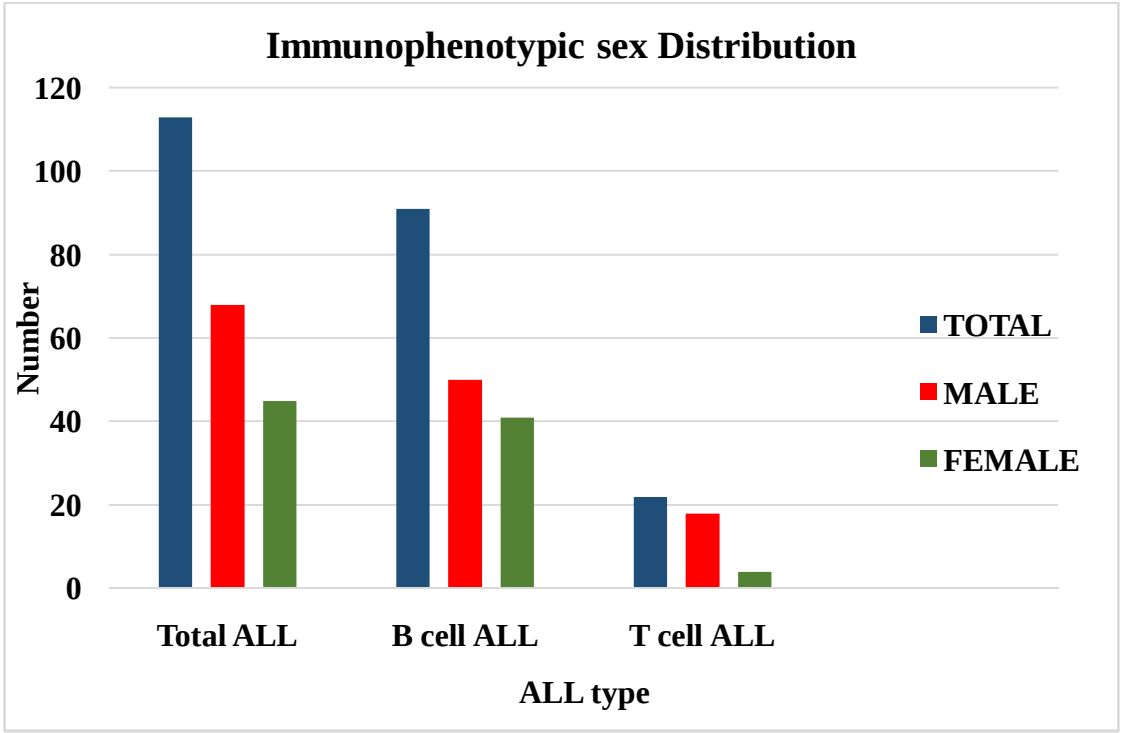


Figure 8

AGE DISTRIBUTION

The age range of this study group wasbetween 1 month to 12 years. Mean age of this study group was 4.92(yrs) with standard deviation of ± 2.96(yrs). The median age group was 4 (yrs). The youngest child was 5 months of age and the oldest was 12 years.

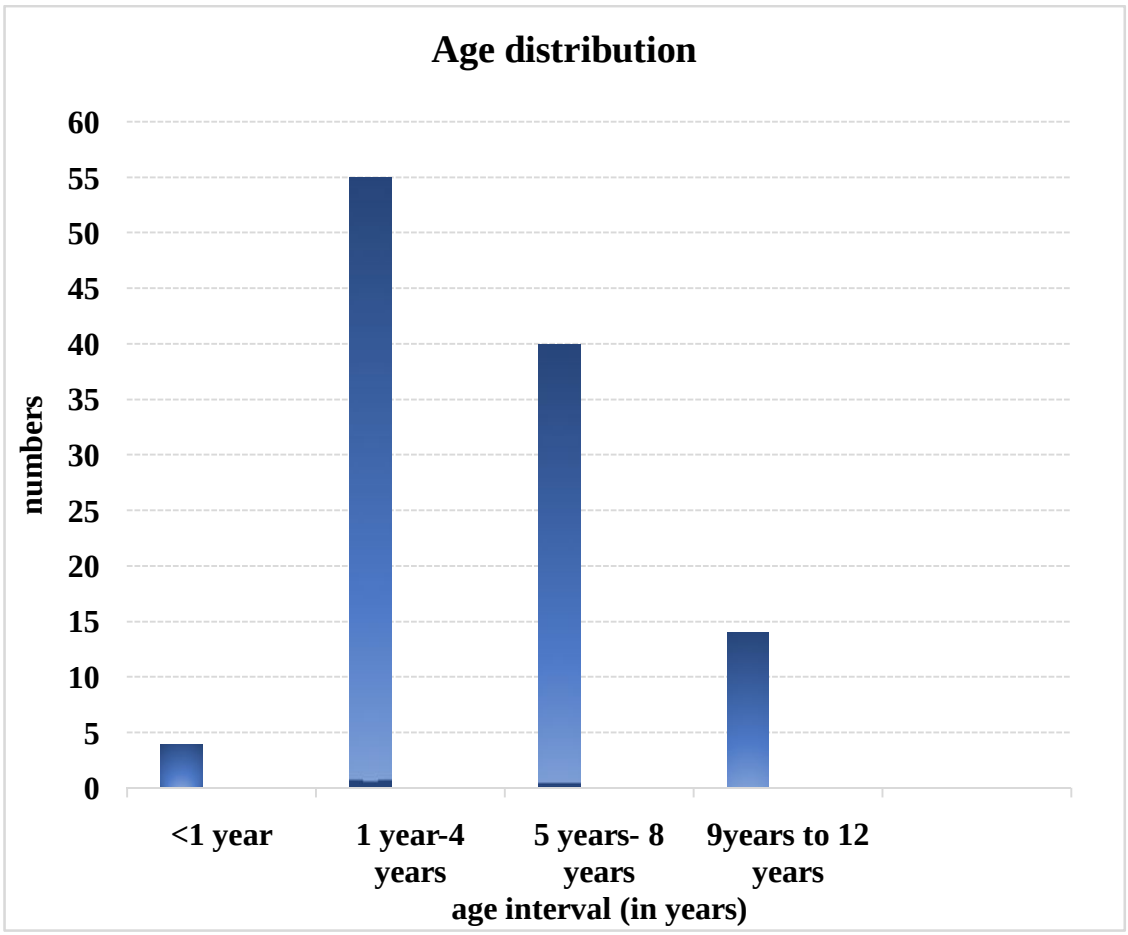


Figure 9

The age distribution was calculated in the interval of <1 years, 1-4 years, 5-8 years and 9-12 years. 3.53 %(4 children) are below 1year of age, 48.67 %(55 children) are between 1-4 years of age, 35.40 %(40children) are between5-8 years and 12.40 %(14chidren) are between 9-12 years of age. Age distribution is illustrated in figure 9.

According to prognostic factor, the age group is divided into 1 to 10 yrs, <1year and >10 years of age group. 89 %(101 children) of children belonged to the good prognostic group (age group 1 year to 10years). 11 % (12children) of children were <1 year and >10 years of age group belong to poor prognostic age group. The age distribution according to prognostic value is shown in figure 10

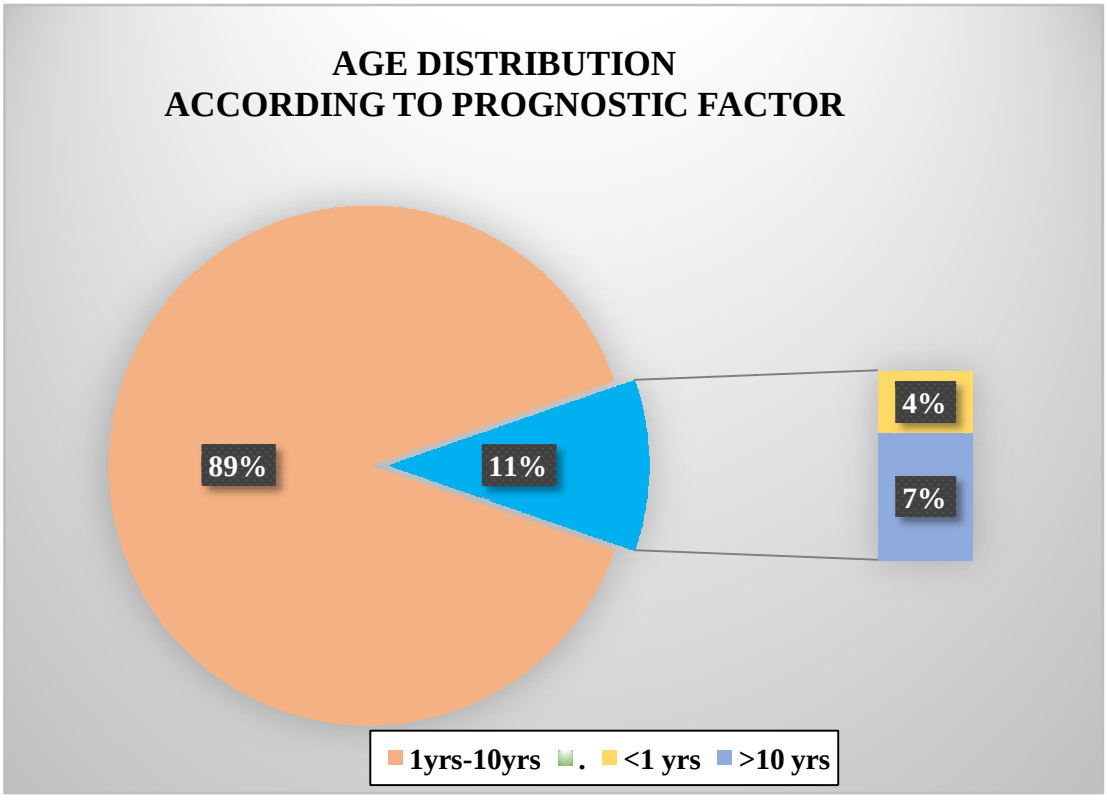


Figure 10

17.7 % (20) of children in this study group were born from consanguineous marriage and 82.3 %(93) were born from non-consanguineous marriage.

85.8 %(97) were born by normal vaginal delivery, 14.2 %(16) were delivered by LSCS for various causes. There were no post-dated deliveries noted in this study, 97.3 %(110) were term at the time of birth and 2.7 %(3) were preterm at the time of birth

92 %(104) children's birth weight was normal and 8 %(9) belonged to low birth weight. There were no children belonging to birth weight of more than 4 kg at the time of birth.

The parameters related to consanguinity, mode of delivery, gestational age, and birth weight and their frequency shown in table 20.

Table 20

PARAMETERS	PERCENTAGE
Consanguineous Non consanguineous	17.7%(20) 82.3%(93)
Term delivery Pre term delivery	97.3(110) 2.7%(3)
Normal vaginal delivery Delivery by LSCS	85.8%(97) 14.2%(16)
Low birth weight Normal birth weight Birth weight >4kg	8%(9) 92%(104) 0%(0)

Two children (1.8%) in this study group had developmental delay, rest of the children (98.2%) attained age appropriate mile stones properly

NUTRITION STATUS

The nutritional status was calculated with weight for age according to WHO growth chart. 73.4 %(83children) of children had normal nutritional status at the time of diagnosis. 22.12 %(25children) children were underweight at the time of diagnosis. 4.42%(5 children) were overweight for their age at diagnosis. Nutritional status and their frequency is shown in figure 11.

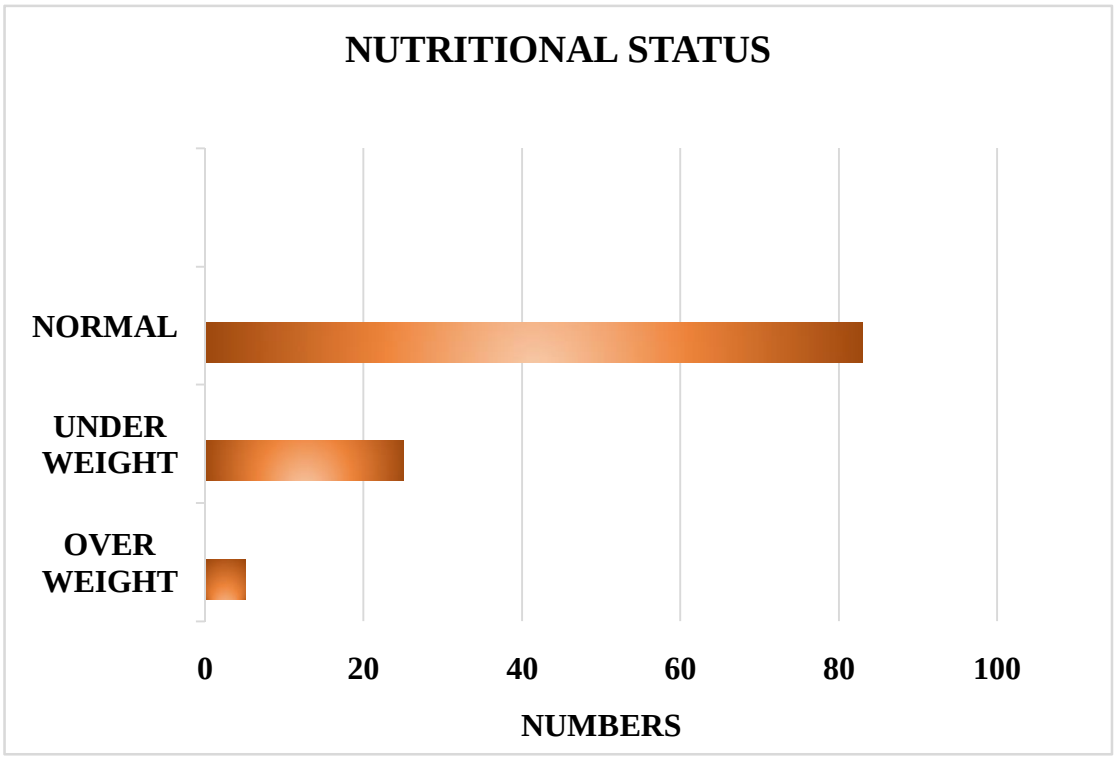


Figure 11

Five children (4.4%) had severe acute malnutrition at the time of diagnosis and four children belonged to thinness who were above 5 years ofage group accounting for about (3.5%) of study population.

Interval between onset of symptoms and diagnosis

The symptoms were noted by history. Time taken for the diagnosis of ALL from the first symptom onset irrespective of hospital admission was calculated in days. Mean duration was 13.13(days) with standard deviation of 12.15(days). The median was 10(days). Minimum duration was 7 days and the maximum interval was 90 days. The descriptive statistics values are shown in table 21.

Table 21

Interval between onset of symptoms and diagnosis	
Parameters	Value (days)
Mean	13.13
SD	±12.15
Minimum	7
Maximum	90

BLOOD GROUP

The ABO blood group and Rh status of study children were analysed. The ABO blood group distribution in total ALL population and inimmunophenotypic distribution is shown in figure 12.

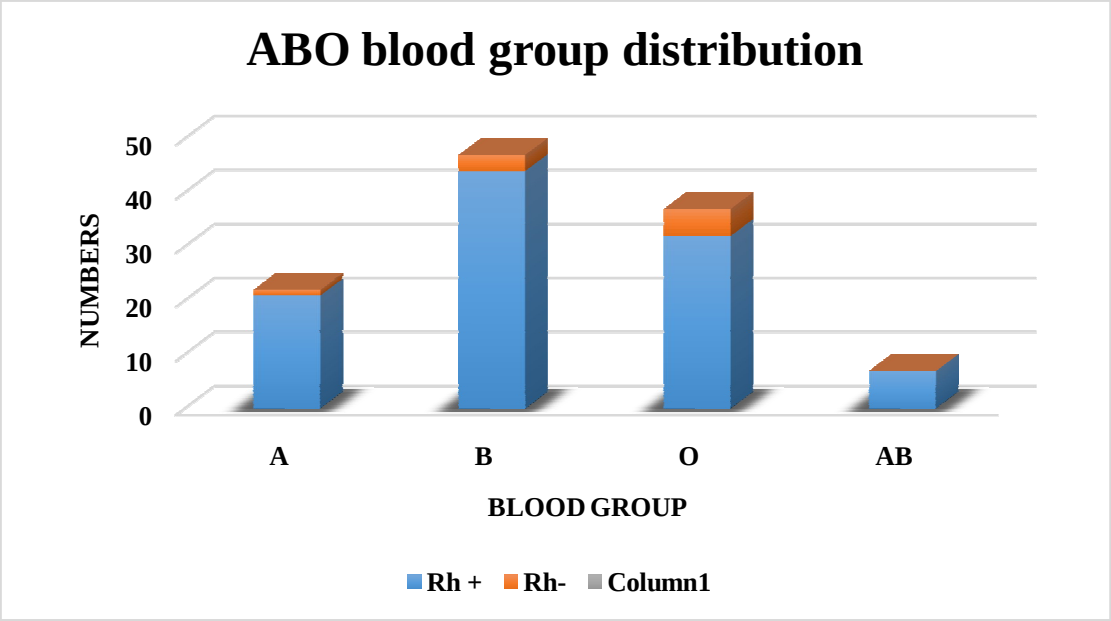


Figure 12

19.46 %(22) of children had A blood group. B blood group consisted of 41.60 %(47children) of study population.32.74 %(37children) had “O” blood group and AB blood group children were 6.20 % (7children). ABO blood group was further divided with Rh status. A+ and A- blood group were 18.58 %(21children) and 0.88 %(1child). B+ and B- blood group were 38.93 %(44 children) and 2.64 %(3children). O+ and O- blood group were 28.31 %(32children) and 4.42 %(5 children) and AB+ and AB- blood group were 6.19 %(7 children) and 0%.

CLINICAL FEATURES

The clinical features were divided into symptoms and signs. The common clinical symptoms were shown in table with frequency of occurrence. 84.1 %(95 children) of study population had fever as the initial symptom followed by abdominal distension (33.6%, 38), the frequency of other symptoms were seen in less than 50% of population. The observed clinical symptoms are tabulated with their frequency in table 22.

Table 22

CLINICAL FEATURES –symptoms		
Symptoms	Frequency	Percentage
Fever	95	84.1%
Fatigue	20	17.7%
Rash	5	4.4%
Paleness	14	12.4%
Icterus	1	0.9%
Anorexia	3	2.7%
Bone pain	13	11.5%
Joint pain	19	16.8%
Difficulty in walking	4	3.5%
Abdominal distension	38	33.6%
Abdominal pain	11	9.7%
Facial puffiness	5	4.4%
Breathlessness	10	8.8%
Seizure	2	1.8%
Headache	4	3.5%

Signs elicited in clinical examination with their frequencies are shown in table23. Pallor (52.2%) and hepatosplenomegaly(52.2%) were seen in more than 50% of population. Followed by lymphadenopathy and bleeding seen in 30% and 20% of study population. Two (1.76%) children had isolated splenomegaly and four (3.5%) children had parotid swelling in their initial clinical examination.

Table 23

CLINICAL FEATURES –signs		
Signs	Frequency	Percentage
Pallor	59	52.2%
Bleeding	24	21.23%
Mucous	10	8.8%
Cutaneous	9	8%
Others	5	4.4%
Tenderness	3	2.7%
Lymphadenopathy	34	30%
Generalised	17	15%
Localised	17	15%
Hepatomegaly	82	72.6%
Splenomegaly	61	54%
hepatosplenomegaly	59	52.2%
Isolated hepatomegaly	23	20.35%
Parotid swelling	4	3.5%

Frequently occurring clinical features and their percentages are illustrated in figure 13.

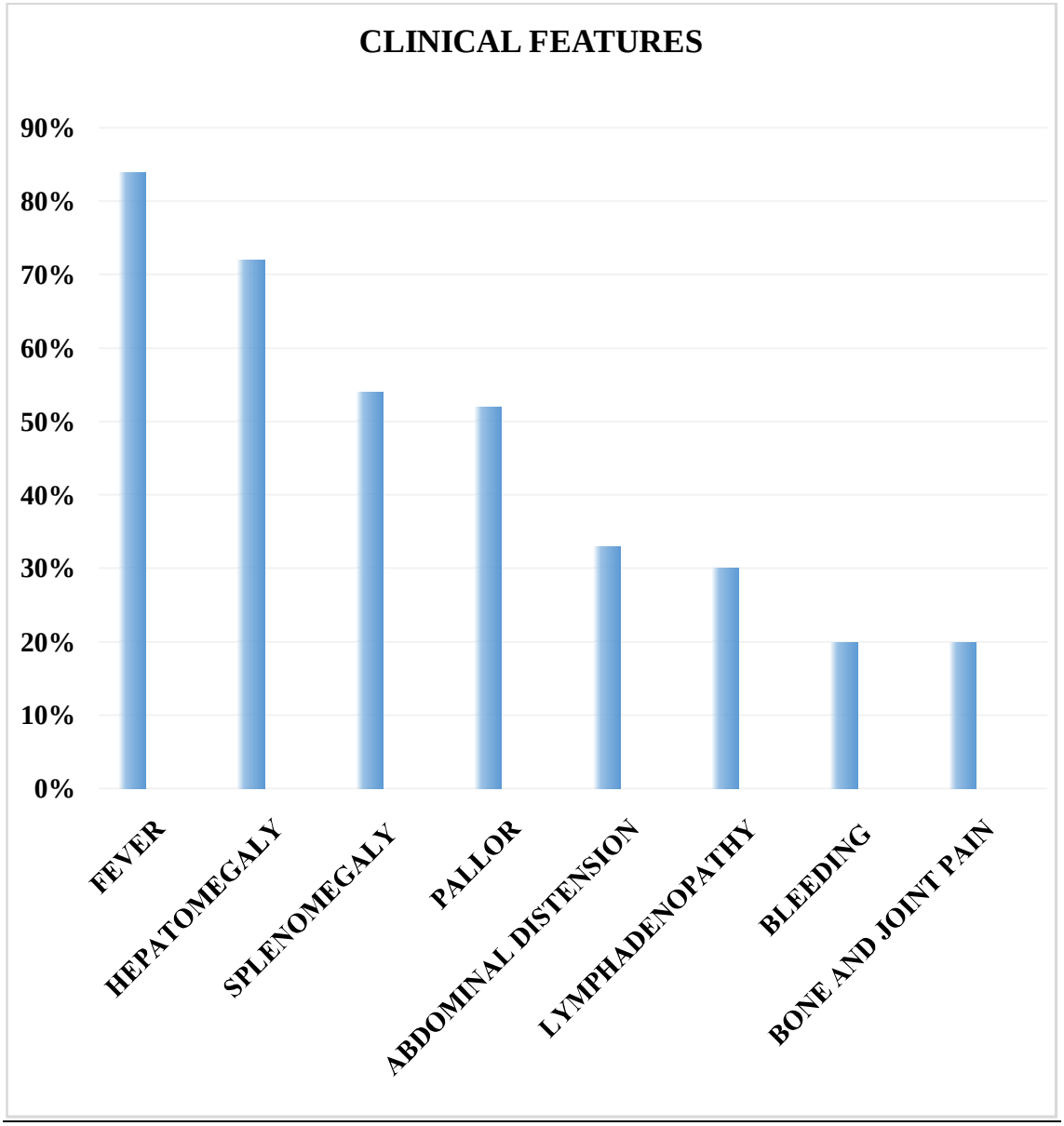


Figure 13

INVESTIGATIONS

Chest x ray was done for all children as an initial investigation. Pleural effusion and mediastinal widening were noted, some children showed pneumonic changes in chest x ray as an initial presentation.1.8 %(2children) children showed mediastinal widening, 2.7 %(3children) showed pleural effusion and 2.7 %(3children) of children had pneumonitis changes in x ray. 92.8% (105) children had normal chest x ray finding. The x ray findings are shown in figure 14.

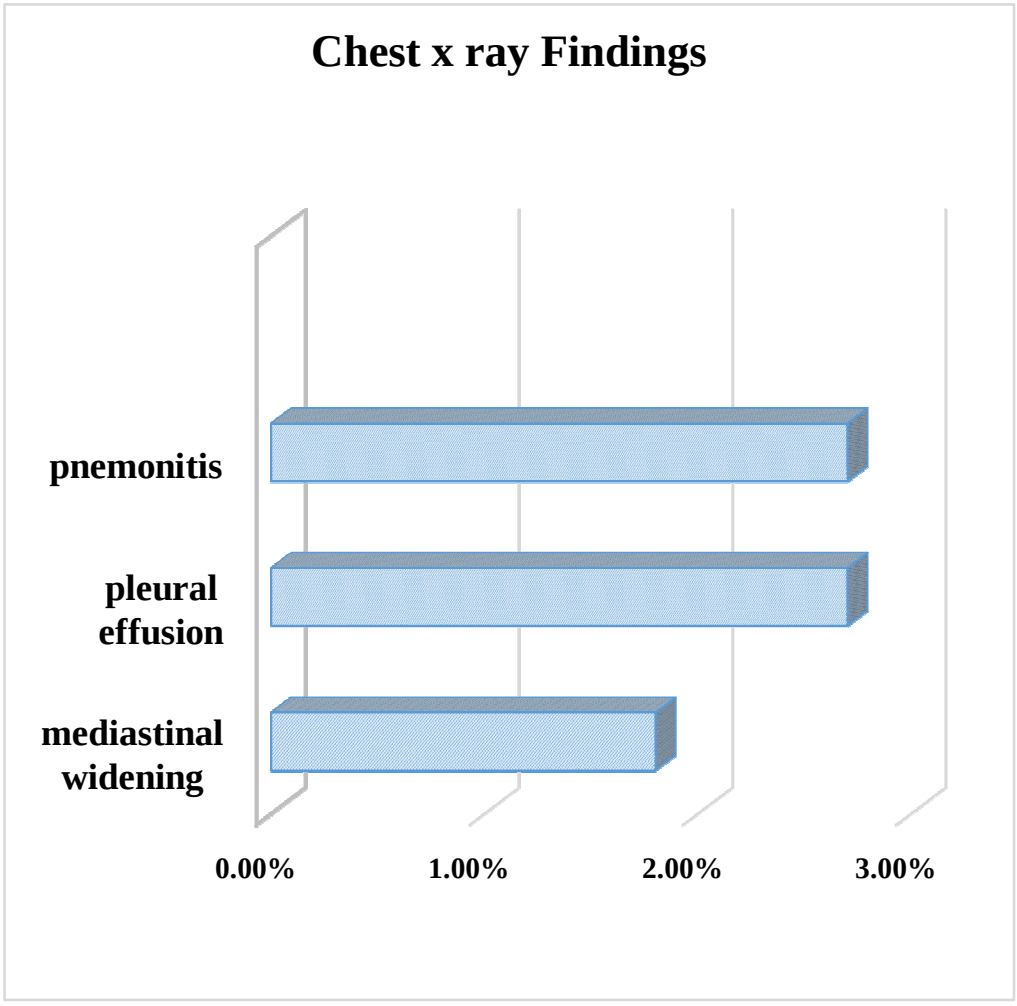


Figure 14

LABORATORY VALUES

HAEMOGLOBIN

The Hb value of less than 11 gm. /dl is considered as anaemia and less 7 gm. /dl is considered as severe anaemia. The mean Hb value is 6.98 with SD of 2.86.Median is 6.8. 90.26 %(102) children in this study group had Hb value of less than 11gm/dl and 54.86 %(62) children had Hb value less than 7 gm. /dl at the time of diagnosis. The descriptive statistics values are shown in table 24.

Table 24

Haemoglobin	
Parameter	Value (mg/dl)
Mean	6.98
SD	2.86
Median	6.8
<7 gm./dl	54.86%
7-11gm/dl	35.39%
>11gm/dl	9.73%

WHITE BLOOD COUNT

The white blood count of this study population varied between 1000/mm^3 to 761000/mm^3. Mean (±SD) of WBC is 55908.8(±91077.40). With median value of 22500. Maximum WBC count was 761000/mm^3.

24.77% of children (28 children) had normal WBC count at the time of diagnosis. 14.15 %of children (16 children) had WBC counts less than 5000/mm3 WBC, 15.04 %of children (17children) had WBC counts more than 100000/mm^3 WBC. In the rest of the study group 54.86 %(62 children) of children had WBC count between 5000/mm^3 to 50000/mm^3 and 15.92 %(18) of children had WBC count between 50000/mm^3 to 100000/mm^3. Distribution of WBC is shown in figure 15.

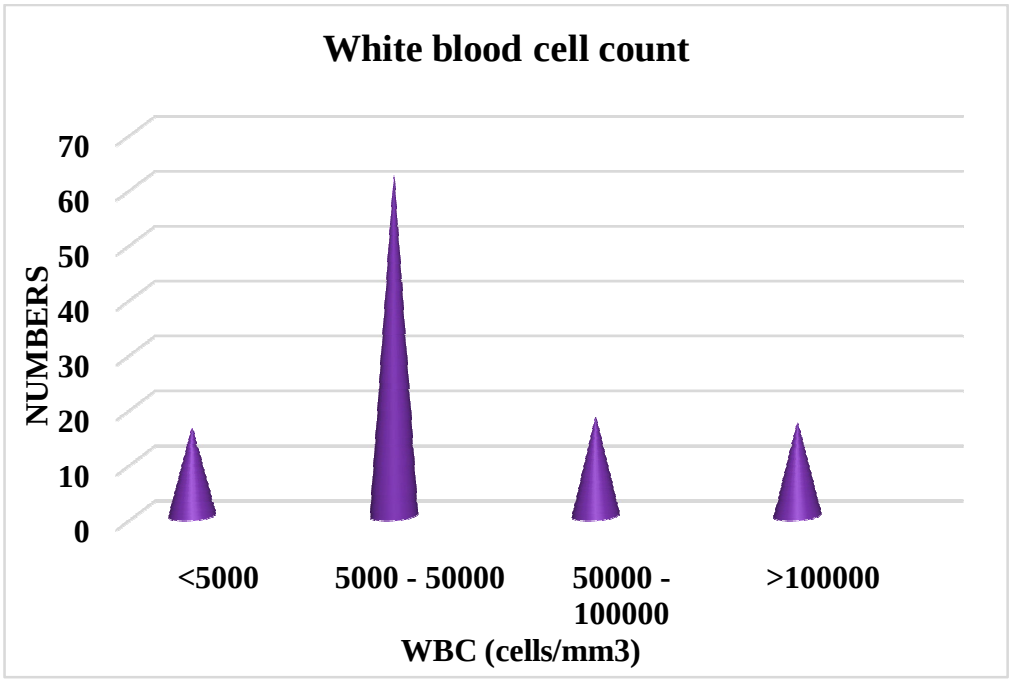


Figure 15

PLATELET

The mean platelet value of this study population was 78518.6 with SD of ±131302.1. The median platelet value was 33000. According to the classification of thrombocytopenia, platelet value was subdivided into less than 20000/mm^3(33.28%,41), between 20000/mm^3 to 50000/mm^3(28.31%,32), between 50000/mm^3 to 100000/mm^3(12.41%,14), between100000/mm^3 to 1.5 lak/mm^3(9.7%,11) and more than 1.5 lakhs/mm^3(13.3%,15). 77% of study population had platelet value of less than 100000 cells/mm^3 at the time of diagnosis. Distribution of platelet values shown in figure 16.

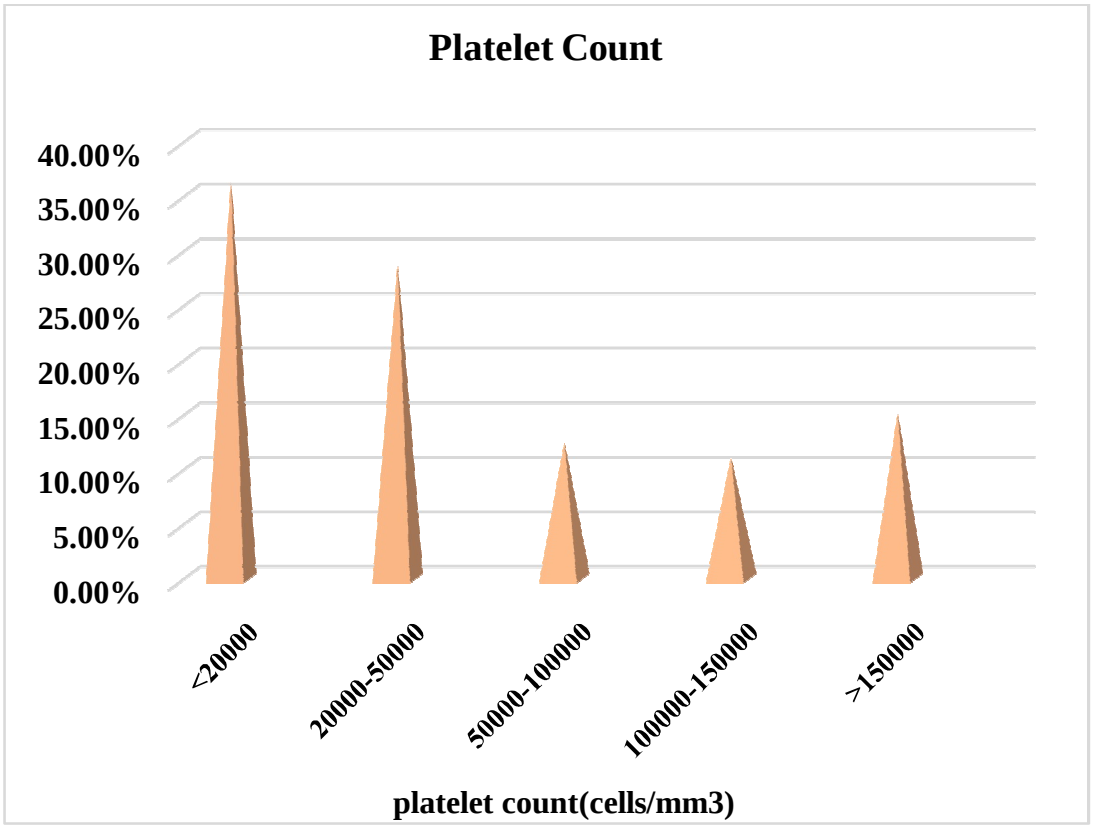


Figure 16

The descriptive statistics values of WBC and platelet are shown in table 25.

Table 25

Parameters	WBC	Platelet
Mean	55908.8	78518.6
SD	±91077.40	±131302.1
Median	22500	33000

PANCYTOPENIA

In this study, pancytopenia was defined as a combination of white blood count less than 4000 $\times 10^9$/L, platelet count less than 100 $\times 10^9$/L and haemoglobin value less than 11gm/dl.

3.5% (4 children) of children had pancytopenia at the time of diagnosis

URIC ACID

Serum Uric acid was done for all the children in this population. Mean uric acid level was 5.46 with Standard deviation of ±2.67. Median value of uric acid was 4.9. Hyperuricemia was calculated according to the age criteria. 28.3% (32 children)of children had elevated uric acid level according to their

age related value. 71.7 %(81children) of children had normal uric acid level at the time of diagnosis.

LDH

Lactate dehydrogenase is used as a prognostic marker and also for diagnostic clue. LDH level was done in all children in this study population .Mean LDH value of this study population was 1003.01 with SD of ±1230.38. The median value was 616. 89.38 %(101children) of children had elevated LDH level at the time of diagnosis.10.61 %(12 children) of children had normal LDH level

Summary of uric acid and LDH value is shown in table 26.

Table 26

URIC ACID and LDH descriptive analysis		
Parameter	Uric acid	LDH
Mean	5.46	1003.01
SD	2.67	1230.38
Median	4.9	616
Elevated level seen in	28.3%	89.38%

Uncommon presentation:

Among the multitude of uncommon presentations of ALL seen in children, hepatitis, tumor lysis syndrome were observed in my studies.

Two children presented as a case of hepatitis which occupies 1.8% of study population.

One (0.9%) child had tumour lysis syndrome at the time of diagnosis

IMMUNOPHENOTYPIC DISTRIBUTION

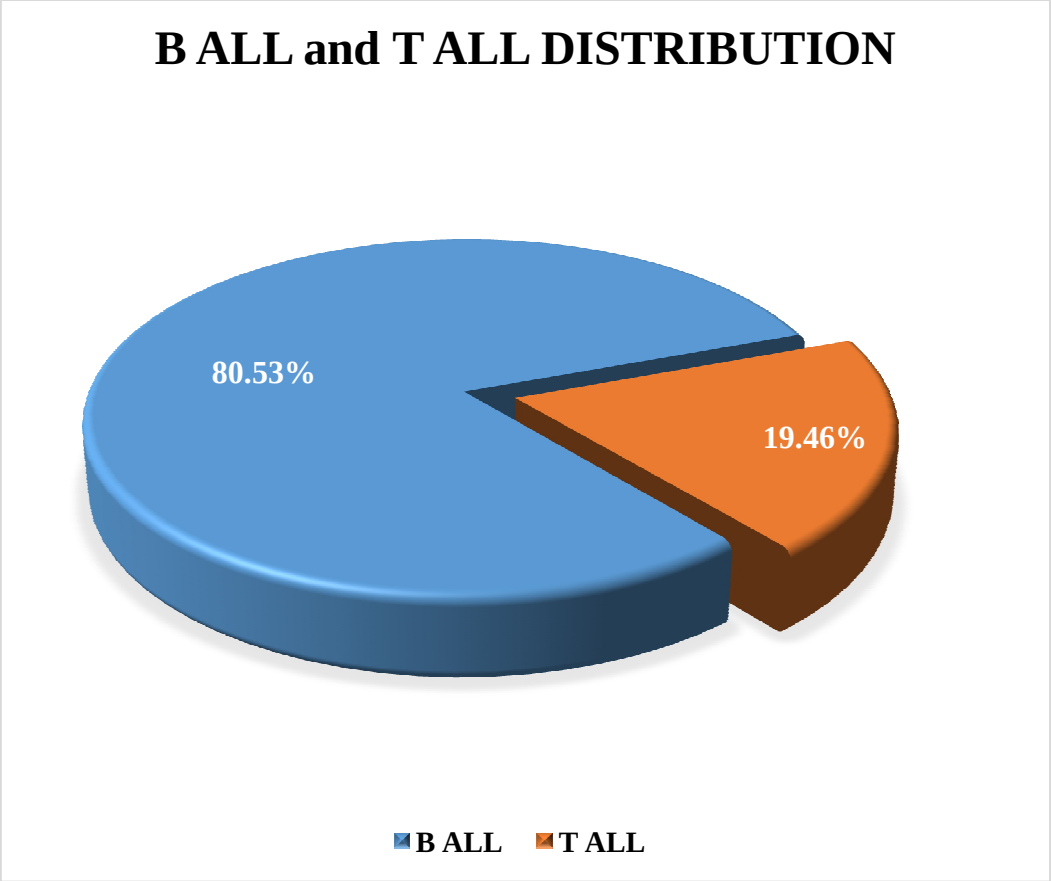
The immunophenotying was done for all children in this study group to confirm the diagnosis.80.53 %(91 children) of children had B cell ALL and rest of the children 19.46%, (22children) had T cell ALL. The frequency of immunophenotyping in this study are shown in table 27.

Table 27

IMMUNOPHENOTYPIC DISTRIBUTION	
ALL TYPE	FREQUENCY
B ALL	76.99%(87)
Pro B ALL	3.5%(4)
T ALL	18.6%(21)
Early T Cell precursor ALL(ETP-ALL)	0.9%(1)

B cell ALL and T cell ALL distribution of this study population is illustrated in figure 17

Figure 17



Four children (3.5%) had pro B ALL and one child (0.9%) had early T cell precursor ALL

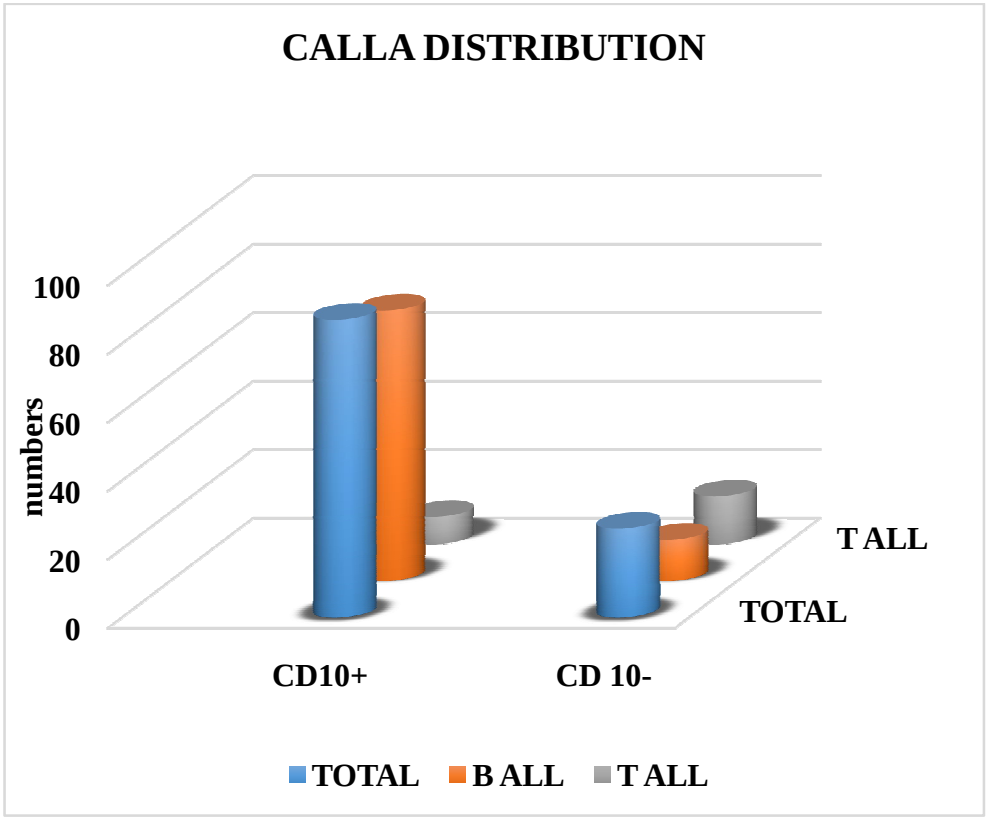
Common ALL Antigen (CALLA) distribution

CD 10 marker was done for all children in this study .In my study among total number of 113 children with ALL, 77 %(87children) had CALLA positivity in their immunophenotying. Remaining 23 %(26 children) of children showed CD10 negativity.

Among children with B cell ALL 80.53% (91 children),86.81 %(79 children) had CALLA positivity and remaining 13.18 %(12children) of children were CALLA negative B cell ALL.

Among 19.5% (22 children) with T cell ALL, 36.36 %(8children) of children had CALLA positivity and remaining fourteen cases (63.63%) were CALLA negative T cell ALL. CALLA distribution in total study population and distribution among immunophenotype is shown in figure 18.

Figure 18



PROGNOSTIC FACTOR DISTRIBUTION

Male sex and age group (less than one year and more than 10 years) were the major prognostic indicators of treatment outcome. Those with Organ infiltration (hepatomegaly, splenomegaly and lymphadenopathy), WBC count more than 50000/ mm3, platelet counts and LDH level had poor prognosis. Distribution of prognostic factor which accounted for poor outcome is shown in table 28.

Table 28

Prognostic factor distribution			
Prognostic factor	ALL(113)	B CELL (91)	T CELL(22)
Age<1yr, >10 yrs.	11%(12)	7.69%(8)	18.18%(4)
Male	60.17%(68)	54.94%(50)	81.81%(18)
Hepatomegaly	72.6%(82)	72.52%(66)	72.72%(16)
Splenomegaly	54%(61)	53.84%(49)	54.54%(12)
Lymphadenopathy	30%(34)	29.67%(27)	31.81%(7)
WBC >50000/mm^3	30.97%(35)	26.37%(24)	50%(11)
PLATELET <100000/mm^3	77%(87)	83.51%(76)	54.54%(12)
Elevated LDH	89.38 %(101)	86.81%(79)	100%(22)

DISCUSSION

Acute lymphoblastic leukemia is characterised by the unrestrained clonal proliferation of haemopoietic precursor cells coupled with aberrant or arrested differentiation. Clinicians depend on the newer diagnostic modalities to diagnose and recognize the association between the morphology and immunophenotype and specific cytogenetic abnormalities. This has led to the development of added treatment modalities based upon specific genetic defects.

ALL accounts for 60-80% of Childhood leukemia, and male preponderance is noted in children with ALL. In my study, a total of 113 children diagnosed to have ALL were included. Out of 113 children 60.17% were male, 39.82% were female. The male: female ratio was 1.58: 1. Male predominance was noted in my study.

In our study 91 children have B-cell ALL. Among them 54.94% were male, 45.05% were female and the male: female ratio for B-cell ALL was 1.21:1. Total children with T-cell ALL were 22, among them 81.81% were male, 18.18% were female and the male: female ratio was 4.5: 1.

Our study supports the finding of definitive male preponderance (60.17%, 68 children) which was as similar as been observed in other studies. It can also occur due to the trend of low female population in our country. The findings of my study were similar to the observations of other studies. The study done by Guru et al(2018) shows male predominance i.e. male: Female

ratio is 3.5:1. The study done by Kulkarni KP et al (2013) [16] showed male predominance with Male: Female ratio of 3.1:1

In our study B-cell ALL(80.53%) was more commonly found in children than T-cell ALL(19.46%) as similar to other studies. Sousa DW et al (2015) [26], conducted a study in 76 patients who were under the age of 19 years and positive for ALL. In their study B cell immunophenotype ALL was found in 89.5% of patients and T immunophenotype ALL was found in 10.5% of patients. B cell immunophenotype is the commonest type in people who are less than 19 years.

In our study peak incidence of paediatric ALL were reported in the age group of 1-4 years of age. The number of children who were affected in this age group was 48.6%. Better prognosis was observed in children belonging to 1-10 years of age.

Sousa DW et al (2015) [26] conducted a study in 76 patients under 19 years of age and diagnosed with ALL. In their study Patients between 1 and 9 years of age were associated with more favourable prognosis similar to my study. Similar observations were made with Guru FR et al (2018) [5], Arya LS et al (2011)[18] and Ahirwar R et al (2018)[29].

82.3% (93 children) were born from non-consanguineous marriage and 17.7% (20 children) were born from consanguineous marriage.

In our study, Majority of children affected with ALL were born through normal vaginal delivery (85.8 %,) .The rest (14.2 %,) were born through LSCS.

Majority of children with ALL had normal birth weight (92 %,) and the rest of 8%, had low birth weight. 97.3% of children were born at term and rest 2.7% children were born at preterm. Mean interval between diagnosis and onset of symptoms was 13.13 ± 12.15 days.

In our study 73.4% (83 children) had normal nutritional status at the time of diagnosis, 22.12% (25 children) were underweight. 4.42 %(5children) were overweight at the time of diagnosis. The study done by Kumar N et al (2017) [34] showed that 50% of children were undernourished at the time of diagnosis and no overweight children were observed in their studies.

In our study B blood group was commonly found in children affected with ALL accounting for 41.5%. In the study done by TavasolianF et al (2014) [33] showed higher number of ALL patients had AB blood group (p value <0.001). Li SY et al (2015)[28] compared the clinical features of ALL in male and female patients in southern china, in their study the most frequently occurring blood group was O blood group, but in my study it was B blood group.

Among the variety of symptoms the commonest complaint recorded in my study was fever, 84.1% have fever. Abdominal distension was the second most common symptom observed in the children in my study, 33.6% had abdominal distension. The other signs and symptoms were fatigue, rash, paleness, icterus, anorexia, bone pain, joint pain, difficulty in walking, abdominal pain, nausea, puffiness, breathlessness, seizures, and headache.

Pandian G et al (2018) [25] did a prospective study in GRH Madurai. In his study fever was the most common symptom as similar to my study. The study of Siddaiahgari SR et al (2015) [6] also had the same observation.

In our study among variety of signs pallor was the sign which was commonly observed in majority of children with ALL. 72.6% of children affected with ALL had hepatomegaly. The second most common sign seen was pallor, 52.2% had pallor. The other signs were bleeding, enlarged lymph nodes which were generalised or localised, hepatomegaly, splenomegaly, hepatosplenomegaly and parotid swelling.

Shalal HH et al (2017), [7] did a retrospective study in 55 patients to show initial presenting features of ALL. In his study fever and pallor were the most common presenting features similar to my study.

Chest x ray was the initial investigation. Pleural effusion, pneumonia, mediastinal widening were the findings seen in chest x ray. In my study2.7% of children had pneumonia.

In our study 1.8% children had mediastinal widening. In the study of Siddaiahgari SR et al (2015) [6], 4.5% of study population had mediastinal involvement.In the study of Shalal HH et al (2017) [7], 7.2% of study population had mediastinal widening.

In our study 2.7% of children had Pleural effusion. In the study of Shalal HH et al (2017) [7], 1.8% of study population had pleural effusion.

Blood investigations such as haemoglobin, WBC count, platelet count, uric acid and LDH were done in my study.

In our study 90.26 % had anaemia at the time of diagnosis and 54.68% with ALL had severe anaemia (haemoglobin value less than 7gms /dl).

Sousa DW et al (2015) [26] conducted a study in 76 patients who were under the age of 19 years and positive for ALL. In their study anaemia was found in 85% of patients. The similar observation was noted in my study, anaemia is seen in almost 90.26% of population among which 54.68 %(62 children) were severely anaemic.

In our study majority of children (57.52%)had WBC counts in the range of 5000-50,000/mm^3.Hyperleukocytosis was observed in 15% with WBC count more than 100000/mm^3.

The study of Shalal HH et al (2017) [7] had 16.4% of study population with hyperleukocytosis. Kong SG, et al (2014) [39] did a study regarding hyperleukocytosis in pediatric ALL at pusan national university hospital. Total enrolment of this study was 104 children. Twenty (19.2%) of 104 children had initial leukocyte count of more than $100x10^9$, 11 patients had a leukocyte count of more than $200x10^9$/L. T cell phenotype, massive splenomegaly and male gender were strongly associated with hyperleukocytosis.

In our study among 113 children, 33.6% had platelet count less than 20,000/mm^3 with severe thrombocytopenia. In the study done by Shalal HH et al (2017) [7] 25.5% of cases had severe thrombocytopenia. Also the study by

Pahloosye A et al (2011) [17] 19% of cases had severe thrombocytopenia in their study population.

In our study 3.5% had pancytopenia at the time of diagnosis. In the study of Kulkarni KP, et al (2013) [42], 11.02% had pancytopenia with ALL, All had better prognosis.

In our study hyperuricemia was observed in 28.3% of children at the time of diagnosis similar to the below mentioned study of Sevinir B et al (2011) [41].The hyperuricemic children in my study have high tumour burden and in such cases the treatment outcome was also affected adversely.

Sevinir B et al (2011) [41] conducted a study to examine the incidence and outcome with ALL and non-Hodgkin's lymphoma. 214 children had ALL in this group in which 26.5% had hyperuricemia and 0.47% had tumorlysis syndrome. Hyperuricemic ALL children of this study had high tumor burden which affected the treatment outcome adversely.

LDH is used as a prognostic marker and in diagnosis; maximum number of children 89.38% had elevated LDH levels.

Uncommon presentations were hepatitis and tumour lysis syndrome which was seen in 1.8% and 0.9% respectively. Tumor lysis syndrome of 32.04% was observed in the study of Siddaiahgari SR et al (2015) [6].

Siddaiahgari SR et al (2015) [6] also noted tumor lysis syndrome in hyperleukocytosis patients comprising 22% of the study population. In my

study 15% of children had hyperleukocytosis, among them only 0.9% showed tumor lysis syndrome.

According to immunophenotypic distribution 80.53% (91 children) had B-cell ALL and 19.46% (22 children) had T-cell ALL. B-cell ALL was the commonest leukaemia observed in my study. This observation was similar to the other studies conducted in India. Siddaiahgari SR et al (2015) [6] observed that the common immunophenotype was B cell ALL. Guru et al (2018) [5] study had 88.6% of B cell ALL.

In our study 77% were CALLA positive and remaining 23% were CALLA negative. This observation was similar with the study done by Pandian G et al (2018) [25] in which 91.7% of ALL showed CD10 positivity. In the study done by Siddaiahgari SR et al (2015) [6], in which 88.75% were CALLA positive and 11.25% were CALLA negative.

In the study of Khan AH et al (2015) [23] 93.1% of B cell ALL expressed CD10 and 45.4% of T cell ALL expressed CD10.

CD 10 distribution according to immunophenotyping was observed in my studies. 86.81% of children in B cell ALL had CD 10 positivity and 36.36 of children in T cell ALL had CD10 positivity. Remaining 13.18% of children in B cell ALL and 63.63% of children in T cell ALL were CD10 negative.

In our study, the children belonging to age group less than 1 year were 3.53% and the children who were more than 10 years are 7.07%, accounting for a total of 11%had poor prognosis. The other important factors determine the

prognosis were Male sex noted in 60.17%, Hepatomegaly noted in 60.17%, Splenomegalynoted in 54%, Lymphadenopathy noted in 30%, WBC more than 50000/mm3 was seen in 30.97%, Platelet less than100000/mm3 was seen in 77% and Elevated LDH was observed in 89.38%. In the study conducted by Arya LS et al (2011) [18] andPahloosye A et al (2011),the above mentioned prognostic factors were as similar as my study which determined the prognosis of the children [17].

LIMITATIONS

- Children who are aged between 1 month to 12 years are alone included in this study.
- It include only 113 children due to availability of cases and time constraint.
- This study is a hospital based study which is not strictly representative of the background population.
- Karyotyping and Cytogenetics abnormalitiesas a prognostic factor of ALL could not be done.

CONCLUSION

ALL was found to be a most frequent childhood haematological neoplasm.

In our study,

- ALL was commonly seen in the age group of 1 - 4 years (48.67%)
- Most of the children (89%) belong to good prognostic age group of 1-10 years
- Male predominance(60.20%) was noted in this study.
- B cell ALL (80.53%) was noted more commonly than T cell ALL (19.46%)
- Majority of the children (77%) with ALL expressed CD10 antigen.
- Most common presenting symptom was fever seen in 84.1% of children and sign was pallor and hepatosplenomegaly seen in 52.2% and 52.2% respectively.
- Most of the children with ALL were anaemic(90.26%). Severe anaemia was noted in 54.68%.
- Hyperleukocytosis was observed in 15%.
- Severe thrombocytopenia was observed in 36%.
- Hyperuricemia was observed in 28%.
- Elevated LDH level was observed in 89.38% at the time of diagnosis.
- Uncommon presentations were hepatitis (1.8%) and tumour lysis syndrome (0.9%)

REFERRANCE AND BIBILOGRAPHY

1. Honig GR. Nelson Text Book of Paediatrics.
2. Bashar, M. A., & Thakur, J. (2017). Incidence and Pattern of Childhood Cancers in India: Findings from Population-based Cancer Registries. Indian Journal of Medical and Paediatric Oncology : Official Journal of Indian Society of Medical & Paediatric Oncology, 38(2), 240–241
3. Bashar MA, Thakur J S. Incidence and pattern of childhood cacers in India: Findings from population-based cancer registries. Indian J Med Paediatr Oncol 2017;38:240-1
4. Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990–2001: incidence and survival. International journal of cancer. 2008 Jun 1;122(11):2607-11
5. Guru FR, Muzamil J, Bashir S. Acute lymphoblastic leukemia, the Indian scenario. MOJ Cell Sci Rep. 2018;5(2):33-7.
6. Siddaiahgari SR, Awaghad MA, Latha MS. Clinical, immunophenotype and cytogenetic profile of acute lymphoblastic leukemia in children at tertiary health care centre in India. Muller J Med Sci Res. 2015;6:112-8.
7. Shalal HH, Mahmood NS, Alchalabi MA. Clinical, hematological, and laboratory presentation of acute lymphoblastic leukemia of children in

Diyala province/Eastern Iraq. International Journal of Research in Medical Sciences. 2017 Sep 28;5(10):4227-33.

8. Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B, Thompson MJ. Clinical presentation of childhood leukaemia: a systematic review and meta-analysis. Archives of disease in childhood. 2016 Oct 1;101(10):894-901.

9. Greer, J. P. (2014). Wintrobe's clinical hematology.

10. Williams EJ. Textbook of Haematology

11. Terwilliger, T., & Abdul-Hay, M. (2017). Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer Journal, 7(6), e577–.12. Zwerdling T. Pediatric acute lymphoblastic leukemia. Hematol Transfus Int J. 2017;5(3):232–238.

13 Jelena Roganovic (May 15th 2013). Acute Lymphoblastic Leukemia in Children, Leukemia Margarita Guenova and Gueorgui Balatzenko, IntechOpen, DOI: 10.5772/55655.

14. Baviskar JB. Incidence of acute and chronic leukemias in rural area at tertiary care teaching hospital: a five years of study. Indian Journal of Pathology and Oncology. 2016;3(4):710-3.

15. Adelman AS, McLaughlin CC, Wu XC, Chen VW, Groves FD. Urbanisation and incidence of acute lymphocytic leukaemia among

United States children aged 0–4. British journal of cancer. 2005 Jun;92(11):2084.

16. Kulkarni KP, Marwaha RK. Significant male preponderance in childhood acute lymphoblastic leukemia in India and regional variation: tertiary care center experience, systematic review, and evaluation of population-based data. Pediatric hematology and oncology. 2013 Sep 1;30(6):557-67.

17. Pahloosye A, Hashemi AS, Mirmohammadi SJ, Atefi A. Presenting clinical and laboratory data of childhood acute lymphoblastic leukemia. Iranian Journal of Pediatric Hematology and Oncology. 2011 Sep 15;1(3):71-7.

18. Arya LS, Padmanjali KS, Sazawal S, Saxena R, Bhargava M, Kulkarni KP, Adde M, Magrath I. Childhood T-lineage acute lymphoblastic leukemia: management and outcome at a tertiary care center in North India. Indian pediatrics. 2011 Oct 1;48(10):785.

19. Francesco Ceppi, Federico Antillon, Carlos Pacheco, Courtney E Sullivan, Catherine G Lam, Scott C Howard & Valentino Conter (2015) Supportive medical care for children with acute lymphoblastic leukemia in low- and middle-income countries, Expert Review of Hematology, 8:5, 613-626.

20. Rajendran A, Bansal D, Marwaha RK, Singhi SC. Tumor lysis syndrome. The Indian Journal of Pediatrics. 2013 Jan 1;80(1):50-4.

21. Mitchell Chris, Hall Georgina, Clarke Rachel T. Acute leukaemia in children: diagnosis and management BMJ 2009; 338 :b2285

22. Bennett JM, Catovsky D, Daniel MT. Proposals for the classification of the acute leukaemias. Br J Haematol 1976; 33: 169- 170.

23. Khan AH, Gupta G, Mehta A, Bashir S, Sharma S, Rasool M. Acute lymphoblastic leukemia in northern India. Indian Journal of Basic and Applied Medical Research. 2015;4(2):372-81.

24. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood. 2016 Jan 1:blood-2016.

25. Pandian G, Sankarasubramaian ML. A study on clinical, immunophenotypic pattern in pediatric acute leukemias in a teaching hospital. International Journal of Contemporary Pediatrics. 2018 Jun 20.

26. Sousa DW, Ferreira FV, Félix FH, Lopes MV. Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. Revista brasileira de hematologia e hemoterapia. 2015 Aug;37(4):223-9.

27. Khalid S, Moiz B, Adil SN, Khurshid M. Retrospective review of pediatric patients with acute lymphoblastic leukemia: a single center experience. Indian Journal of Pathology and Microbiology. 2010 Oct 1;53(4):704.

28. Li SY, Ye JY, Meng FY, Li CF, Yang M. Clinical characteristics of acute lymphoblastic leukemia in male and female patients: A retrospective analysis of 705 patients. Oncology letters. 2015 Jul 1;10(1):453-8.

29. Ahirwar R, Nigam R.K, Parmar D. A study of leukemias Profile in central India.Trop J Path Micro 2018;4(2):182-187.

30. Sidhom, I., Shaaban, K., Soliman, S., Ezzat, S., El-Anwar, W., Hamdy, N., & Mansour, M. T. (2008). Clinical significance of immunophenotypic markers in pediatric T-cell acute lymphoblastic leukemia. Journal of the Egyptian National Cancer Institute, 20(2), 111-120.

31. Anoop, C., Appaji, L., Padma, M., Arunakumari, B., Avinash, M., Suma, T., Rekha, V. (2016). Profile of acute lymphoblastic leukemia in children upto 2 years of age – Study from a Tertiary Cancer Centre from South India, Bangalore. Pediatric Hematology Oncology Journal, 1(2). doi:10.1016/j.phoj.2016.10.021

32. Badira, C. P., Sneha, T., Nirav, T., Subramaniam, P., Prashant, T., Sumeet, G., . . . Shripad, B. (2016). Clinical profile and outcome of early T-precursor (ETP) acute lymphoblastic leukemia (ALL) in a tertiary care cancer centre. Pediatric Hematology Oncology Journal, 1(2).

33. Tavasolian F, Abdollahi E, Vakili M, Amini A. Relationship between ABO blood group and Acute Lymphoblastic Leukemia. Iranian journal of pediatric hematology and oncology. 2014;4(1):1.

34. Kumar, N., Srinivasan, A., Loganathan, A., Bharadwaj, R., & Scott, J. X. (2017). Nutritional profile of children with acute Lymphoblastic Leukemia- data from a tertiary care centre from south India. Pediatric Hematology Oncology Journal, 2(2). doi:10.1016/j.phoj.2017.11.092.

35. Higashiyama Y, Kojima C, Kubota M, Nagai A, Watanabe KI, Adachi S, Usami I. Longitudinal nutritional assessment in acute lymphoblastic leukemia during treatment. Pediatrics International. 2014 Aug;56(4):541-6.

36. Totadri S, Trehan A, Kaur A, Bansal D, Jain R. Does distance between residence and treating center impact outcome in childhood acute lymphoblastic leukemia? Report from a tertiary care center in North India. Pediatric Hematology Oncology Journal. 2016 Jan 1;1(2):S11.

37. Caughey RW, Michels KB. Birth weight and childhood leukemia: A meta-analysis and review of the current evidence. International Journal of Cancer. 2009 Jun 1;124(11):2658-70.

38. Milne E, Greenop KR, Metayer C, Schüz J, Petridou E, Pombo-de-Oliveira MS, Infante-Rivard C, Roman E, Dockerty JD, Spector LG, Koifman S. Fet al growth and childhood acute lymphoblastic leukemia: findings from the childhood leukemia international consortium. International journal of cancer. 2013 Dec 15;133(12):2968-79.

39. Kong SG, Seo JH, Jun SE, Lee BK, Lim YT. Childhood acute lymphoblastic leukemia with hyperleukocytosis at presentation. Blood research. 2014 Mar 1;49(1):29-35.

40. İrken G, Oren H, Oniz H, Cetingul N, Vergin C, Atabay B, Gulen H, Turker M, Kantar M, Yılmaz S. Hyperleukocytosis in childhood acute lymphoblastic leukemia: complications and treatment outcome. Turk J Hematol. 2006 Sep 5;23:142-6.

41. Sevinir B, Demirkaya M, Baytan B, Güneş AM. Hyperuricemia and tumor lysis syndrome in children with non-Hodgkin's lymphoma and acute lymphoblastic leukemia. Turkish Journal of Hematology. 2011 Mar 1;28(1).

42. Kulkarni KP, Marwaha RK. Acute lymphoblastic leukemia with pancytopenia at presentation: Clinical correlates, prognostic impact, and association with survival. Journal of pediatric hematology/oncology. 2013 Oct 1;35(7):573-6.

43. Kumar P, Trehan A, Bhalla AK, Marwaha RK, Bansal D. Growth in Children Treated for Acute Lymphoblastic Leukemia: Single Institution Report from North India. Indian Journal of Hematology and Blood Transfusion. 2016 Mar 1;32(1):39-45.

44. Alavi S, Ashraf H, Rashidi A, Hosseini N, Abouzari M, Naderifar M. Distribution of ABO blood groups in childhood acute leukemia. Pediatric hematology and oncology. 2006 Jan 1;23(8):611-7.

45. Al-Sudairy R, Al-Nasser A, Alsultan A, Ahmari AA, Abosoudah I, Al-Hayek R, Al-Harbi T, Al-Manjomi F, Al-Harbi M, Al-Ghamdi H, Al-Shahrani M. Clinical characteristics and treatment outcome of childhood acute lymphoblastic leukemia in Saudi Arabia: A multi-institutional retrospective national collaborative study. Pediatric blood & cancer. 2014 Jan;61(1):74-80.

46. Satyanarayana L, Asthana S, Labani SP. Childhood cancer incidence in India: A review of population-based cancer registries. Indian pediatrics. 2014 Mar 1;51(3):218-20.

CLINICAL PROFILE OFACUTE LYMPHOBLASTIC LEUKEMIA INCHILDREN.

PROFORMA FOR THE STUDY

Name: Age: Sex:

Urban/Rural:

Inpatient no: Hematology no:

Adresss:

Detailed History of presenting illness

Fever

Bleeding manifestation

(Epistaxis, petechiae, purpura, ecchymosis, Gum bleed,Melena)

Swelling(cervical, axillary, inguinal)

Pallor

Abdominal distension

Bone pain

General body pain

Joint pain

Inability to walk

Breathlessness

Abdominal pain

Seizure

Others

Past history:

Developmental history:

Immunization history:

Family history:

Treatment history:

Clinical Examination:

General examination

Pallor

lymphadenopathy:(localised, generalised)

Icterus:

Pedal edema:

Cyanosis :

Clubbing :

Head to foot examination

Oral cavity

Eyes

Ears

Limbs

Bone and joints

Spine

Skin

External bleeds (skin, mucocutaneous)

Genitals (testicular swelling)

ANTHROPOMETRY

Weight: Height/length:

Head Circumference: Mid arm circumference

VITAL SIGNS

Heart rate: Respiratory rate:

Blood pressure: Body temperature:

SYSTEM EXAMINATION:

Cardiovascular system

Respiratory system

Abdomen examination

Central nervous system

Investigations

Peripheral smear

Bone marrow cytology

Flow cytometry

Complete hemogram

Haemoglobin

Total white blood cell count

Differential Count

Platelets count

Pcv

Rbc

Mcv

Mch

Mchc

Rdw

Renal function test

Blood sugar

Serum urea

Serum creatinine

Serum electrolyte

Serum sodium

Serum potassium

Liver function test

SGOT

SGPT

Serum bilirubin

Serum Amylase

Serum calcium

Serum phosphorus

Serum Uric acid

Serum LDH

Viral marker

Urine analysis

Urine albumin, sugar, deposits

Stool analysis

Stool for occult blood

Chest x ray	X ray long bones
Ultrasonography abdomen	
Echocardiography	CSF analysis
Blood group	Others

PATIENT INFORMATION SHEET

PLACE OF STUDY: Institute Of Child Health and Hospital for Children, Egmore, Chennai-8

NAME OF INVESTIGATOR: Dr.P.Balamurugan.

NAME OF PARTICIPANT AGE:

SEX:

HOSPITAL NO: HEMATOLOGY NO:

STUDY TITLE:Clinical Profile of Acute Lymphoblastic Leukemia

We request you to participate in the study

Aim of the study

This study aims to determine the clinical profile of acute lymphoblastic leukemia in children, The purpose of this study is to determine the varied presentation of acute lymphoblastic leukemia

Methodology

Your child's symptoms and signs will be elicited and necessary blood investigations, bone marrow aspiration study, x ray study, computed tomography study and cerebrospinal fluid analysis will be done.

Can I refuse to participate in the study ?

Participation in the study is purely voluntary. You may refuse to participate or withdraw from the study at any time . in both cases the treatment and care your child receives from this hospital will not be affected in any mannaer.

Benefits and harms of participating in the study

Your child will not benefits directly by participating in this study. But by way of participating in this study, your child is contributing to updation of

science which may benefit her/him and all other patients with this disease in future.

Confidentiality

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Subject rights

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled. The results of the special study may be intimated to you at the end of the study period .

Can I contact the investigator?

If you wish further information regarding your child's rights as a research participant, You can contact the investigator in the mobile number or address mentioned below

Principal investigator : Dr.P.Balamurugan

Mobile number : 9698364693

Contact address : post graduate student M.D., pediatrics , institute of child health and hospital for children, egmore, Che nnai.

Signature of investigator Signature of participant

Date:

Place:

தகவல் படிவம்

ஆய்விடம் : அரசு குழந்தை நல ஆராய்ச்சி நிலையம் மற்றும் குழந்தை நல மருத்துவமனை , எழும்பூர் , சென்னை 8.

ஆய்வாளர் : மருத்துவர் . பெ .பாலமுருகன்

பங்குபெறுபவரின் பெயர் : வயது : பாலினம் :

மருத்துவமனை எண் : குருதியியல் எண்:

ஆய்வு தலைப்பு :

தீவிரமான நிணநீர்ம இரத்தப் புற்றுநோயால் பாதிக்கப்பட்ட குழந்தைகளுக்கு ஏற்பட்ட அறிகுறிகள் , வேதியல் மாற்றங்கள் மற்றும் கண்டறிந்த முறைகள் பற்றிய ஆய்வு.

நான் தங்கள் குழந்தையும் இந்த ஆய்வில் பங்குபெற கேட்டுகொள்கின்றோம்.

செய்முறை:

தங்கள் குழந்தைக்கு ஏற்பட்ட அறிகுறிகள் மற்றும் உடல் மாற்றங்கள் கேட்டு அறியப்படும் மேலும் தேவையான இரத்த பரிசோதனைகள் செய்யப்படும் ,தேவை ஏற்படின் தங்கள் முழு ஒப்புதலுடன் எலும்பு மச்சை ஆய்வு , முதுகுஎலும்பு வழியாக எடுக்கப்பட்ட மூளை நீர் பரிசோதனை ,ஊடுகதிர் படம் ,கணினிவழி உடலுறுப்பு ஊடுகதிர்ப்படம் போன்றவை செய்யப்படும்

இரகசியத்தன்மை:

உங்கள் குழந்தையைப் பற்றிய தனிப்பட்ட விவரங்கள் யாருக்கும் தெரிவிக்காமல் பாதுகாக்கப்படும்.

ஆய்வில் பங்கேற்க மறுத்தல்:

இந்த ஆய்வில் பங்கு பெறுவது உங்கள் தனிப்பட்ட விருப்பமே. ஆய்வு ஆரம்பித்தபின் விருப்பம் இல்லை என்றால் தாங்கள் விலகிக்கொள்ளலாம். அவ்வாறு விலகுவதானது தங்கள் குழந்தையின் சிகிச்சைக்கு எவ்வித பாதிப்பையும் உருவாக்காது

பங்கேற்பதின் இலாப நஷ்டங்கள்:

இந்த ஆய்வில் பங்கேற்பதால் தங்கள் குழந்தைக்கு எந்த பலனும் இல்லை .ஆய்வின் முடிவுகள் ஆய்வு நடக்கும்போதோ(தேவை ஏற்படின்) அல்லது ஆய்வு முடிந்த பின்னரோ தங்களுக்கு தெரிவிக்கப்படும். அந்த முடிவுகள் தங்கள் குழந்தை மற்றும் இந்த நோயால் பாதிக்கப்பட்ட மற்ற குழந்தைக்களின் சிகிச்சைக்கு பேருதவியாக இருக்கக்கூடும்.

பங்கேற்பவர் உரிமை:

தங்கள் குழந்தை பற்றிய விவரம் தெரிய ஆய்வு மருத்துவரை அணுகலாம்.

ஆய்வாளரின் பெயர் :மருத்துவர் .பெ. பாலமுருகன்

கைபேசி எண்: 9698364693

முகவரி : முதுநிலை பட்டமேற்படிப்பு மாணவர் ,அரசு குழந்தை நல ஆராய்ச்சி நிலையம் மற்றும் குழந்தை நல மருத்துவமனை , எழும்பூர் , சென்னை 8.

ஆய்வாளரின் கையொப்பம் பெற்றோரின் கையொப்பம்

நாள்

இடம்

INFORMED CONSENT FORM

STUDY PLACE: Institute Of Child Health And Hospital For Children, Egmore, Chennai-8

TITLE OF THE STUDY: Clinical Profile Of Acute Lymphoblastic Leukemia In Children

NAME OF THE INVESTIGATOR : Dr.P.Balamurugan.

NAME OF THE PARTICIPANT: AGE: SEX:

HOSPITAL NUMBER: HEMATOLOGY NO:

1. I have read and understood this consent form and the information provided to me regarding the participation in the study.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I will allow my child to cooperate with the investigator and undergo clinical tests subjected during the study whole heartedly.

6. I have been advised about the risks associated with my participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study in the past.

9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

11. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

12. I have understand that my identity will be kept confidential if my data are publicly presented

13. I have had my questions answered to my satisfaction.

14. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document. For adult participants:

Name and signature / thumb impression of the participant /parents/guardian

Name _____ Signature_____

Date_____

Name and Signature of impartial witness:

Name _____ Signature_____

Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

ஒப்புதல் படிவம்

ஆய்விடம் : அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர் , சென்னை 8

ஆய்வாளர் : மருத்துவர் . பெ .பாலமுருகன்

பங்குபெறுபவரின் பெயர் : வயது : பாலினம் :

மருத்துவமனை எண் : குருதியியல் எண்:

ஆய்வு தலைப்பு :

தீவிரமான நிணநீர்ம இரத்தப் புற்றுநோயால் பாதிக்கப்பட்ட குழந்தைகளுக்கு ஏற்பட்ட அறிகுறிகள் , வேதியல் மாற்றங்கள் மற்றும் கண்டறிந்த முறைகள் பற்றிய ஆய்வு.

1) எனக்கு தரப்பட்ட ஆராய்ச்சியில் பங்கு பெறுவோர்க்கான தகவல் படிவத்தை முழுமையாக படித்து புரிந்து கொண்டேன்.
2) ஆராய்ச்சியின் தன்மை முழுமையாகவும் விரிவாகவும் எடுத்துரைக்கப்பட்டது
3) எனது எல்லா கேள்விகளுக்கும் விடையளிக்கப்பட்டது .
4) ஆய்வாளர் என் உரிமைகளையும் , பொறுப்புகளையும் நன்கு விளக்கினார்
5) நன் , என் குழந்தை , ஆய்வாளருக்கு முழு ஒத்துழைப்பு கொடுக்கவும் , பரிசோதனை செய்துகொள்ளவும் அனுமதிக்கிறேன்
6) என் குழந்தைக்கு இரத்த பரிசோதனை , எலும்பு மச்சை ஆய்வு , ஊடுகதிர் படம் , கணினி வலி ஊடுகதிர் படம் மற்றும் தேவைக்கான பரிசோதனைகள் செத்துக்கொள்ள முழு மனதுடன் சம்மதம் தெரிவிக்கிறேன்.
7) எனது குழைந்தை ஆராய்ச்சியில் பங்கேற்பதால் ஏற்படும் சாதக பாதங்களை ஆய்வாளர் விளக்கிக்கூற அறிந்துகொண்டேன்

8) எப்பொழுது வேண்டுமானாலும் என் குழந்தையை இந்த ஆய்வில் இருந்து விலக்கி கொள்ளலாம் என்பதை அறிவேன் . அவ்வாறு விளக்கிக்கொள்வதால் குழந்தைக்கு கொடுக்கப்படும் சிகிட்சையில் எந்த மாற்றமும் இருக்காது என அறிந்து கொண்டேன்

9) இந்த ஆய்வுக்காக பெறப்படும் என் குழந்தையின் தகவல்களை ஆய்விதழ்களிலேயோ , கருத்தரங்கிலேயோ வெளியிடுவதில் எனக்கு எந்தவித மறுப்போ , ஆட்சேபணையோ இல்லை .

10) என் குழந்தையின் தன் அடையாளங்கள் ஆய்விதழ்களிலேயோ, கருத்தரங்கிலேயோ வெளியிடப்பட மாட்டாது என் எனக்கு உறுதியளிக்கப்பட்டது .

11) எனக்கு இந்த ஆராய்ச்சி குறித்தன சந்தேகம் இருந்தால் உடனே ஆய்வாளரை கேட்டு தெளிவுபடுத்தி கொள்ளலாம் என உறுதியளிக்கப்பட்டது

12) இந்த ஒப்புதல் படிவத்தில் கையொப்பமிடுவதின் மூலம் இந்த படிவத்தில் உள்ளவை யாவும் எனக்கு தெளிவாக எடுத்துரைக்கப்பட்டது , அதை நான் நன்கு புரிந்து கொண்டேன் என தெரிவித்துக்கொள்கிறேன்

நோயாளியின் பெற்றோர் / பாதுகாவலர்

பெயர் கையொப்பம்/ பெருவிரல் சுவடு தேதி

ஆராய்ச்சியாளர்

பெயர் கையொப்பம்/ பெருவிரல் சுவடு தேதி

சாட்சி 1

பெயர் கையொப்பம்/ பெருவிரல் சுவடு தேதி

சாட்சி 2

பெயர் கையொப்பம்/ பெருவிரல் சுவடு தேதி

cases	sex(m:1,f:2)	age(years)	symptom to diagnosis interval(days)	blood group	current treatment	autoimmune hypothyroidism(no:1,yes:2)	multifocal thyroid malignancy(no:1,yes:2)	consanguinity(no:1,yes:2)	swelling(no:1,yes:2)	FH (presence)	birth weight(n:1,l:2)	developmental delay(no:1,yes:2)	fever(no:1,yes:2)	fever duration(days)	fatigue(no:1,yes:2)	pulmonary(no:1,yes:2)	bone pain(no:1,yes:2)	joint pain(no:1,yes:2)	difficulty in walking(no:1,yes:2)	rashes(no:1,yes:2)	anaemia(no:1,yes:2)	abd distension(no:1,yes:2)	abd pain(no:1,yes:2)	vomiting(no:1,yes:2)	facial puffiness(no:1,yes:2)	convulsion(no:1,yes:2)	seizures(no:1,yes:2)	jaundice(no:1,yes:2)	pallor(no:1,yes:2)	mucosal bleeding(no:1,yes:2)	cutaneous bleeding(no:1,yes:2)	bleeding(no:1,yes:2)	tenderness(no:1,yes:2)	LP(no)	LP(yes)	wbc(<3,>3)	rbc(<3,>3)	hb(<3,>3)	mod wasting(no:1,yes:2)	pneumonia(no:1,yes:2)	pleural effusion(no:1,yes:2)	parotid swelling(no:1,yes:2)	blast (no:1,yes:2)	type of all	cd10(p:1,n:2)	wbc	hb	platelet	uric acid	ldh	tb(p:1,n:2)	hepatitis(p:1,n:2)
case 1	2	2	7	o+	2	1	0	2	1	1	1	1	1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	2	9000	1.50	54000	3.0	335	2	2
case 2	1	2	12	b+	1	1	0	2	1	1	1	1	1	14	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	42000	6.80	31000	5.3	440	2	2
case 3	2	8	10	a+	1	0	1	2	1	1	1	1	1	10	1	2	1	1	2	2	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	1	41900	1.10	21000	5.7	1211	2	2
case 4	2	9	30	o+	1	0	1	2	1	1	1	1	1	30	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	1	3400	1.70	46000	2.3	858	2	2
case 5	1	12	30	o+	1	0	1	2	1	1	1	1	1	30	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	1	3500	6.90	1170000	4.3	599	2	2
case 6	2	4	2	o+	1	1	0	2	1	1	1	1	1	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	2	5500	7.60	112000	4.1	313	2	2
case 7	2	2	4	o+	1	1	0	1	2	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	1	69700	4.70	47000	5.2	7312	2	1
case 8	1	10	15	o+	1	0	1	2	1	1	1	1	1	15	2	1	1	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	14300	12.90	7000	6.7	517	2	1
case 9	1	8	20	o+	1	0	1	2	1	1	1	1	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	t	2	3500	1.70	3000	3.1	1056	2	2
case 10	1	4	2	o+	2	1	0	2	1	1	1	1	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	23600	7.20	18000	2.4	292	2	2
case 11	2	8	10	o+	1	0	0	2	1	1	1	1	1	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	40600	5.70	5000	5.2	450	2	2
case 12	1	4	4	o+	1	1	0	2	1	1	1	1	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	1	65800	5.40	14000	4.8	910	2	2
case 13	1	2	15	b-	1	1	0	2	2	1	1	1	1	15	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	4500	7.60	11400	5.7	377	2	2
case 14	2	7	7	o+	1	0	1	1	1	1	1	1	1	7	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	51000	7.10	11900	3.1	870	2	2
case 15	1	2	7	o+	1	1	0	2	2	1	1	1	1	7	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	1900	3.40	2006	7.3	560	2	2
case 16	1	3	5	o+	1	1	0	2	1	1	1	1	2	0	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	2	29000	6.70	39000	6.2	1120	2	2
case 17	1	1	1	o+	1	1	0	2	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	85500	3.20	9000	11.5	1852	2	2
case 18	1	11	7	b+	1	0	1	2	2	1	1	1	2	0	2	1	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	53000	9.40	227000	4.4	560	2	2
case 19	1	3	10	o+	1	1	0	2	1	1	1	1	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	1	47500	6.40	22900	5.6	960	2	2
case 20	1	2	10	o+	1	1	0	2	1	1	1	1	1	10	2	1	2	2	1	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	9500	6.00	6000	3.3	565	2	2
case 21	1	2	7	o-	1	1	0	2	1	1	1	1	1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	2	43000	6.90	23000	11.9	1299	2	2
case 22	1	3	11	ab+	1	1	0	2	1	1	2	1	1	14	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	37000	3.80	4000	6.5	373	2	2
case 23	2	8	5	a+	2	0	1	2	2	2	2	2	2	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	16300	8.70	10000	2.4	234	2	2
case 24	2	3	30	b-	2	1	0	2	1	1	1	1	1	30	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	13100	6.40	15000	3.1	615	2	2
case 25	1	3	5	o+	2	1	0	2	1	1	1	1	1	5	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	98000	5.90	23000	8.4	570	2	2
case 26	1	2	4	o-	1	2	0	2	1	1	2	1	1	4	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	21200	5.10	20000	6.5	490	2	2
case 27	1	8	5	o+	1	0	1	2	1	1	1	1	1	5	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	1	166000	8.10	12900	9.0	560	2	2
case 28	1	5	30	b+	1	0	1	2	1	1	2	1	1	30	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	21400	5.20	15900	4.1	1599	2	2
case 29	1	1	1	o+	1	2	0	2	1	1	1	1	1	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	52100	9.60	33000	9.9	4066	2	2
case 30	1	6	5	b+	1	0	1	1	1	1	1	1	1	5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	1800	2.50	25000	11.9	118	2	2
case 31	1	8	20	a+	1	0	1	2	1	1	1	1	1	20	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	2	17300	3.40	27900	4.8	310	2	2
case 32	2	6	12	o-	2	0	1	2	1	1	1	1	1	12	1	2	1	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	41200	5.20	5000	5.3	545	2	2
case 33	2	1	3	ab+	2	1	0	2	1	1	1	1	1	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	3900	3.10	2400	1.8	610	2	2
case 34	2	5	10	a+	2	0	1	2	1	1	2	1	1	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	b	1	34000	9.30	1	4.2	414	2	2
case 35	1	8	3	o+	1	0	1	2	1	1	2	1	1	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	16600	5.10	11000	3.0	475	2	2
case 36	1	10	7	o-	1	0	1	1	1	1	1	1	1	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	2	149000	13.70	68000	8.1	1170	2	2
case 37	1	6	14	b-	1	0	1	2	1	1	1	1	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	3200	10.20	48900	5.6	412	2	2
case 38	1	12	7	b+	1	0	1	2	1	1	1	1	1	7	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	212096	8.30	20000	8.5	2415	2	2
case 39	2	3	20	o+	1	1	0	2	1	1	1	1	1	20	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	1000	8.70	28900	4.1	595	2	2
case 40	1	1	7	b+	1	1	0	2	1	1	1	1	1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	pro B	2	19450	7.40	23900	2.5	950	2	2
case 41	2	2	3	b-	1	1	0	2	1	1	1	1	1	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	146900	10.40	14900	11.6	840	2	2
case 42	2	8	60	o+	1	0	1	2	1	1	2	1	1	60	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	5500	4.10	9000	3.3	573	2	2
case 43	2	1	4	o+	1	2	0	2	2	1	1	1	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	24000	7.30	49900	4.9	456	2	2
case 44	2	4	10	b+	2	1	0	2	1	1	1	1	1	10	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	40700	7.90	49900	4.1	456	2	2
case 45	1	10	7	b+	1	0	1	2	2	1	1	1	1	7	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	1	111400	10.50	170000	3.9	1190	2	2
case 46	2	6	7	o+	1	0	2	2	2	1	1	1	1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	32700	3.30	52900	6.8	312	2	2
case 47	1	9	14	a+	2	0	1	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	2	19900	14.00	140900	4.3	1158	2	2
case 48	2	3	2	b+	1	1	0	2	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	19600	4.90	13900	4.7	750	2	2
case 49	1	8	4	o+	1	0	1	2	2	1	1	1	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	2	124900	8.40	111000	3.9	949	2	2
case 50	2	3	7	o+	1	1	0	2	2	2	2	2	2	7	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	84000	6.90	19900	7.3	345	2	2
case 51	1	3	30	o+	1	1	0	2	1	1	1	1	1	30	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	55000	4.30	72000	5.8	909	2	2
case 52	1	6	90	o+	1	0	1	1	1	1	1	1	1	90	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	49700	5.50	140000	6.9	1577	2	2
case 53	2	2	12	a+	1	1	0	1	1	1	1	1	1	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	t	2	19200	10.90	281000	6.7	1152	2	2
case 54	1	11	15	ab+	1	0	1	2	1	1	1	1	1	15	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	35200	7.60	19000	7.0	1121	2	2
case 55	1	8	15	b+	1	0	1	2	1	1	1	1	1	15	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	210000	5.60	189000	2.2	755	2	2
case 56	1	4	10	o+	1	1	0	2	1	1	1	1	1	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	2	1300	4.30	27900	2.9	180	2	2
case 57	1	7	7	o+	1	0	1	2	2	1	1	1	1	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	t	2	215400	8.20	63600	6.0	452	2	2
case 58	2	3	5	o+	2	1	0	2	2	2	2	2	1	5	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	9300	7.90	14000	6.3	221	2	2
case 59	1	3	4	o-	1	1	0	2	1	1	1	1	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	9800	4.10	67000	3.2	456	2	2
case 60	2	8	20	b+	2	0	1	2	1	1	1	1	1	20	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	19700	10.70	99000	3.4	976	2	2
case 61	2	2	4	b+	1	1	0	2	1	1	1	1	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	145700	5.70	11000	5.7	1403	2	2
case 62	1	3	7	ab+	2	1	0	2	1	1	1	1	1	7	1	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	b	1	43600	8.90	139000	4.8	9114	2	2

case 63	1	9	30	a+	1	0	1	1	1	1	1	1	1	30	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	1	1	2	2	2	2	2	2	2	b	1	20200	13.10	10000	3.6	1887	2	2
case 64	2	1	60	a+	1	3	0	2	2	1	1	1	1	60	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	b	1	78000	5.50	90700	1.2	480	2	2
case 65	1	7	14	b+	1	0	1	2	2	1	1	1	2	0	1	2	2	2	2	2	2	1	2	2	1	2	2	2	1	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	t	1	247500	5.70	18900	10.6	674	2	2
case 66	1	2	7	b+	1	2	0	2	1	1	1	1	2	0	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	t	2	14900	9.80	580000	3.0	840	2	2
case 67	2	4	10	a+	2	3	0	2	1	1	1	1	1	10	2	1	2	2	2	2	2	1	1	2	2	2	2	2	1	2	2	1	2	2	2	2	1	2	1	1	1	2	2	2	2	1	b	1	4360	5.40	15000	8.4	767	2	2
case 68	2	2	4	ab+	2	1	0	1	1	1	1	1	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	b	1	26000	2.30	14000	13.3	334	2	2
case 69	1	4	20	b+	1	1	0	2	1	1	1	1	1	20	2	2	1	2	2	2	2	1	2	2	2	1	2	2	1	2	2	1	2	2	2	2	1	2	1	1	1	2	2	1	2	1	b	1	15000	6.90	16000	4.0	883	2	2
case 70	2	6	14	b+	2	0	1	2	1	1	1	1	1	14	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	2	2	1	2	2	b	1	10400	4.70	74000	5.4	650	2	2
case 71	1	3	15	a+	1	3	0	2	1	1	1	1	1	15	2	1	2	1	1	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	pro b	2	73400	6.80	38000	7.4	1972	2	2
case 72	1	4	21	b+	1	3	0	2	1	1	1	1	1	21	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	1	2	1	b	1	261000	6.90	171000	5.4	461	2	2
case 73	1	6	7	b+	1	0	1	2	1	1	1	1	1	7	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	2	2	1	2	2	b	1	1800	3.90	14000	3.2	310	2	2
case 74	1	5	15	a+	1	0	2	2	1	1	1	1	1	15	1	2	1	2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	1	1	2	2	2	2	1	2	2	t	1	149000	11.90	103000	5.4	450	2	2
case 75	2	6	7	o+	2	0	1	2	1	1	1	1	1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	1	2	1	b	1	14500	3.80	18000	3.1	530	2	2
case 76	2	5	30	o+	2	0	1	2	1	1	1	1	1	30	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	1	2	1	1	2	2	2	2	2	1	1	1	2	2	1	2	2	pre b	1	6700	6.50	6000	7.8	650	2	2
case 77	1	6	14	o-	1	0	1	1	1	1	2	2	2	0	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	2	2	2	2	1	2	1	b	1	47600	11.70	246000	2.5	912	2	2
case 78	1	2	21	o+	1	3	0	2	1	1	1	1	1	21	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	b	1	122000	6.60	53000	2.8	442	2	2
case 79	1	4	3	a+	1	3	0	1	1	1	1	1	1	3	2	1	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	pro b	2	16000	11.00	13000	6.4	1851	2	2
case 80	1	8	8	b+	1	0	1	2	2	1	1	1	1	8	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	2	2	b	1	9200	2.30	42000	6.3	380	2	2
case 81	1	2	15	o+	1	1	0	2	1	1	1	1	1	15	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	t	1	32000	15.20	560000	6.5	1212	2	2
case 82	1	2	30	b+	1	2	0	1	1	1	1	1	1	30	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	1	2	2	b	1	2000	4.00	240000	2.9	171	2	2
case 83	1	1	20	a+	2	1	0	2	1	1	1	1	1	20	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	1	7400	3.40	16000	4.6	650	2	2
case 84	1	4	15	b+	1	3	0	1	1	1	1	1	1	15	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	1	2	2	2	2	2	1	1	1	1	2	2	2	2	2	b	2	2500	7.10	3500	3.9	840	2	2
case 85	2	2	20	a+	1	3	0	1	1	1	1	1	1	20	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2	b	1	46300	4.90	76000	2.4	230	2	2
case 86	1	5	7	a+	1	0	1	2	1	1	1	1	1	7	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	1	3200	4.00	51000	5.8	450	2	2
case 87	1	9	14	o+	2	0	4	2	1	1	1	1	2	0	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	t	1	14000	14.50	420000	4.3	511	2	2
case 88	2	4	10	a+	1	1	0	2	1	1	1	1	1	10	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	t	2	12000	7.60	112000	4.2	671	2	2
case 89	2	7	3	b+	1	0	4	2	1	1	1	2	1	7	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	2	t	2	91700	10.00	50000	14.9	1230	2	2
case 90	2	4	10	a+	2	1	0	2	1	1	1	1	1	10	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	pro b	2	12000	7.60	112000	4.2	671	2	2
case 91	1	4	20	b+	1	1	0	2	1	1	1	1	1	20	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	b	1	14300	9.30	41000	4.8	614	2	2
case 92	2	2	5	b+	2	2	0	2	1	1	1	1	1	5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	1	b	1	250000	11.20	32000	10.5	600	2	2
case 93	1	1	15	b+	1	3	0	1	1	1	1	1	2	0	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	1	1	1	1	2	2	2	2	1	t	2	264700	7.70	44000	5.4	560	2	2
case 94	2	9	21	ab+	1	0	1	2	1	1	1	1	2	0	2	2	1	2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	2	2	2	2	1	2	1	1	1	2	2	2	2	2	etp t	2	22500	6.50	140000	4.3	1200	2	2
case 95	2	2	7	o+	1	1	0	1	1	1	1	1	1	7	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	2	200000	5.50	46000	7.2	1270	2	2
case 96	1	5	10	b+	1	0	3	2	1	1	1	1	1	10	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	1	9100	3.70	19000	14.0	301	2	2
case 97	1	7	20	o+	2	0	4	2	1	1	1	1	1	20	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	2	b	1	18900	14.20	310000	5.3	1160	2	2
case 98	2	1	8	o+	1	1	0	2	1	1	1	1	1	8	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	1	2	2	1	2	2	2	2	2	1	1	1	2	1	2	2	1	b	1	27300	4.70	313000	4.3	281	2	2
case 99	1	7	9	o+	1	0	1	2	1	1	1	1	1	9	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	2	2	1	2	1	2	2	2	1	1	1	2	2	2	2	2	t	2	162000	5.70	50000	8.4	970	1	2
case 100	2	9	10	b+	1	1	0	2	1	1	1	1	1	10	2	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	1	b	1	53800	8.50	16000	6.4	5335	2	2
case 101	2	2	5	b+	1	3	0	2	1	1	1	1	1	5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	b	1	6600	8.70	26000	5.6	560	2	2
case 102	1	6	5	ab+	1	0	1	2	1	1	1	1	1	5	2	2	1	2	2	2	2	2	1	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	2	2	2	2	2	t	1	2000	3.30	5000	6.5	587	2	2
case 103	1	4	15	o+	2	1	0	2	1	1	1	1	1	15	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2	1	b	1	72000	5.10	42000	2.7	764	2	2
case 104	1	2	14	b+	1	1	0	2	1	1	1	1	2	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	b	1	78500	7.70	935000	3.6	870	2	2
case 105	2	8	10	b+	1	0	1	2	1	1	1	1	1	10	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	2	2	2	2	1	b	1	136000	3.40	32000	4.9	927	2	2
case 106	1	7	7	b+	1	0	1	2	2	1	1	1	1	7	2	2	2	2	2	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	2	b	1	17500	9.30	1000	2.3	780	2	2
case 107	1	3	7	o+	1	1	0	1	1	1	1	1	1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	1	3800	8.00	158000	4.5	970	2	2
case 108	1	6	7	b+	1	0	1	2	1	1	1	1	1	7	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	1	9100	3.10	19000	2.9	301	2	2
case 109	2	10	14	b+	1	0	1	2	1	1	1	1	2	0	2	1	1	1	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	b	1	6000	9.60	211000	4.9	326	2	2
case 110	1	8	20	o+	1	0	1	2	1	1	1	1	1	20	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2	2	b	1	18200	6.50	57000	2.6	487	2	2
case 111	1	6	7	b+	1	0	1	2	1	1	1	1	1	7	1	2	2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	1	2	1	1	1	2	2	2	2	2	b	1	30000	7.40	25000	4.7	551	2	2
case 112	1	3	20	o+	1	1	0	2	1	1	1	1	1	20	2	2	2	2	2	1	2	1	2	2	2	2	2	2	1	1	1	1	1	1	1	2	2	2	1	2	2	2	2	2	2	2	b	1	1700	5.40	7000	5.7	672	2	2
case 113	2	7	10	b+	1	0	1	2	1	1	1	1	1	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	2	2	2	2	2	b	2	70500	7.90	34000	8.3	676	2	2